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Role of protective *Pelargonium sidoides* root extract and curcumin on mushroom poisoning ; An experimental study in rats

Unsal V*[1], Kuruta EB[2], Gungor M[2], Aksan M Emrah[2]

***Corresponding author:**

Unsal V

[1]Gaziosmanpa a University Medicine faculty Department of Biochemistry ,Tokat, Turkey
[2]Sutcu Imam University, Medicine of Faculty, Department of Biochemistry, Kahramanmaras, Turkey

A b s t r a c t

Phalloidin is a cyclic heptapeptide containing cysteine amino acids. The toxicity of phallodin is attributed to the sulfur atom of the sulfur in the indole ring of the molecule and it is responsible for acute gastroenteritis occurring during the initial period of poisoning. Pelargonium sidoides, reinforcing the immune system, antiviral, has antibacterial properties as well as antioxidant properties. The aim of this study is to investigate the protective role of *Pelargonium sidoides*and Curcumin against mushroom poisoning.

28 Wistar albino rats were divided into four groups. Group I; Along the study, 0.2 ml saline was administered intraperitoneally to therats .Group II (phalloidin, 0.5 mg / kg) were administered for 5 days of study. Group III : From the beginning to the end of the study, 0.5 mg / kg phalloidin i.p.,0,2 ml/kg *Pelargonium sidoides*were administered orally. Group IV : From the beginning to the end of the study, 0.5 mg / kg phalloidin intraperitoneally,0.2 ml/kg Curcumin were administered orally. At the end of the study, the rats were sacrificed. The blood of the rats was taken . n serum Superoxide dismutase (SOD), Glutathione peroxidase (GSH-Px), Paraxonase (PON), Arylesterase (ARE) ,Adenosine Deaminase (ADA) , Xhanthine oxidase (XO),Protein Karbonyl (PC), Malondialdehyde(MDA), Nitric oxide (NO), were measured by spectrophotometry.

In Group II, MDA, , PC levels and XO activity increased significantly compared to Group I. ($p<0.05$).PS and Curcumin treatment ameliorated some enzyme levels (SOD, GSH-px, PON, ADA) in serum with phalloidin induced rats. Values of Group III approached Group I.

Phalloidin increases toxic ROS. *Pelargonium sidoides*and Curcumin are antioxidant, antitoxic. And They such as silibin can protective against mushroom poisoning.

Keywords: Mushtoom poisoning, Curcumin, Pelargonium Sidoides, oxidative stress, antioxidants, Antitoxic

Introduction

Mushroom poisoning is a serious clinical condition that is seen worldwide, especially in rainy conditions [1]. Although several mushroom species can be responsible, those of the genus Amanita cause the most severe clinical damage. The most poisonous mushroom toxins are produced by Amanita phalloides [2]. Phallotoxins are a group of bicyclic heptapeptides from poisonous mushrooms. Phalloidin, binds to actin filaments much more tightly than to act in monomers [3]. The toxicity of the molecule is due to the sulfur atom in the indole ring and it is responsible for the acute gastroenteritis that occurs during the initial period of poisoning [4].

In recent years different treatment methods of mushroom poisoning have been researched. Intoxicated patients and therapy contains supportive care and countless numerous combinations of drugs, including antibiotics (Benzylpenicillin, ceftazidime) and antioxidants (Silybin ,N-acetylcysteine, vitamin C, vitamin E, α-lipoicacid. e.g) therapy. However, most do not have enough clinical activity in the treatment process. Thus, in recent years, special attention has been given to studies of the pathophysiology of mushroom poisoning [5]. *Pelargonium sidoides* is a medicinal herb that is traditionally used in South Africa. It is used in the treatment of upper respiratory tract infections and gasrointestinal disorders [6-7-8-9]. The beneficial effects of *P. sidoides* can be attributed to its antiviral, antibacterial, antioxidant and immunomodulatory activities [10-11-12-13]. Curcumin has been shown to have anti-inflammatory, hypoglycemic, antioxidant, wound healing and antimicrobial activities. Comprehensive preclinical studies in recent years have revealed cur cumin's therapeutic potential against human diseases [14-15]. Antioxidative properties of curcumin are

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well documented. Curcumin is a potent scavenger of reactive oxygen species including superoxide anion radicals and hydroxyl radicals. It has also been reported to inhibit lipid peroxidation. Curcumin administration in rats has reduced the oxidative stress caused by toxic substances such as arsenic, gentamicin and acetaminophen [16-17]. Toxic substances increase the ROS and they are caused oxidative stress ROS, including superoxide, hydrogen peroxide (H_2O_2), hydroxyl, and nitric oxide are induced. [18-19-20-21]. In the study, malondialdehyde (MDA), protein carbonyl (PC), and xanthine oxidase (XO), which enhance ROS, were evaluated. Several enzymes involved in ROS clearing such as superoxide dismutase (SOD), glutathione peroxide (GSH-Px), paraoxonase (PON) and arylesterase (ARE) and adenosine deaminase (ADA) were evaluated.

Our aim in this study was to investigate oxidant and antioxidant status in phalloidin-induced rats. Herein, we disclose further results of relevance to the antioxidant profile of *Pelargonium sidoides* and Curcumin besides that Can it be used for treatment of mushroom poisoning?

Materials and Methods

Biochemical Analyses

The study was approved by the local ethical committee. A total of 28 male Wistar albino rats, 5.5–6 months old and weighing 250–300 g, were used in the study. The rats were randomly divided into four groups each consisting of 7 rats. Experimental groups and protocol are shown in Table 1. The experimental animals were housed at 18-22 °C, under a 12 h light/12 h dark cycle and had free access to standard pellet diet for rats and to tap water ad libitum throughout the study. No rat was given antibiotics. All surgical procedures were performed under xylazine/ketamine anesthesia in sterile conditions. All rats were sacrificed after the experimental procedures. Blood samples were drawn into heparin-free tubes for biochemical analyses. After centrifugation (2000 xg for15 min at +4 ºC), serum samples were stored frozen at - 20ºC.

Table.1 : Dose and experimental groups

	N	First day	The second day	The third day	Fourth day	Fifth day
Group I : Control	7	Saline (i.p)-0,2 ml	Saline (i.p)- 0,2 ml	Saline (i.p)- 0,2 ml	Saline (i.p)- 0,2 ml	Saline (i.p)- 0,2 ml
Group II : Pha	7	Pha (i.p, 0,5 mg/kg)- 0,2 ml	Pha (i.p, 0,5 mg/kg)- 0,2 ml	Pha (i.p, 0,5 mg/kg)- 0,2 ml	Pha (i.p, 0,5 mg/kg)- 0,2 ml	Pha (i.p, 0,5 mg/kg)- 0,2 ml
Group III:Pha+ PS	7	Pha (i.p, 0,5 mg/kg)- 0,2 ml + PS (oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + PS (oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + PS (oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + PS (oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + PS (oral,0,2 ml)
Group IV: Pha+ Cur	7	Pha (i.p, 0,5 mg/kg)- 0,2 ml + Cur(oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + Cur(oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + Cur(oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + Cur(oral,0,2 ml)	Pha (i.p, 0,5 mg/kg)- 0,2 ml + Cur(oral,0,2 ml)

a-Abbreviations ;Pha : Phalloidin **PS** : Pelargonium sidoides**, Cur** : curcumin, **i.p** : ntraperitoneal

Chemicals

Phalloidin was obtained from Ali Baba Com. (China). The *Pelargonium sidoides* root extract solution and Curcumin extract was obtained from the medical pharmacy. (Respectively; Abdi brahim ilaç firması , Berko laç ve Kimya San. A.). Determinations of the following parameters were made in the serum samples using commercial chemicals supplied by Sigma (St. Louis, USA).

MDA

TBARS level was determined by a method [22] based on reaction with thiobarbituric acid (TBA) at 90^0C–100^0C. In the TBA test reaction, MDA or MDA-like substances and TBA react to produce a pink pigment with an absorption spectrum maximum at 532 nm. There action was performed at pH 2–3 and 98^0C for 15 min. The sample was mixed with two volumes of cold 10% (w/v) TBA to precipitate the protein. The precipitate was pelleted by centrifugation and an aliquot of the supernatant was reactedwith an equal volume of 0.67% (w/v) TBA in a boiling water-bath for 10 min. After cooling, the absorbance was read at 532 nm. MDA levels were expressed μmol/L, according to the calibration curve prepared from measurements with a standard solution(1,1,3,3-tetramethoxypropane).

SOD

The principle of the total SOD (EC 1.15.1.1) activity method is based, briefly, on the inhibition of nitroblue tetrazolium (NBT) reduction by O_2·generated by xanthine/xanthine oxidase system [23]. Activity was assessed in the ethanol phase of the serum after 1.0 ml ethanol/chloroform mixture (5/3, v/v) was added to the same volume of the plasma and centrifuged. One unit of SOD was

defined as the enzyme amount causing 50% inhibition in the NBT reduction rate. Activity was expressed as units per milliliter (U/ml).

GSH-Px

GSH-Px activity was measured by the method of Paglia and Valentine [24]. The enzymatic reaction in the tube-containing nicotinamide adenosine dinucleotide phosphate, reduced glutathione, sodium azide and glutathione reductase was initiated by the addition of H_2O_2 and the change in absorbance at 340 nm was monitored by a spectrophotometer. Enzymatic activity was expressed in units. U/L.

PC

The carbonyl contents were determined spectrophotometrically based on the reaction of carbonyl group with 2,4-dinitrophenylhydrazine to form 2,4-dinitrophenylhydrazone [25] . 2,4-Dinitrophenylhydrazine was the reagent originally used for proteins subjected to metal–catalyzed oxidation. The results were given as nmol/ml.

PON and ARE

The determination of paraoxonase activity is based on the spectrophotometric measurement of p-nitro phenol levels released as a result of the enzymatic hydrolysis of paraoxon [26-27]. The measurement of paraoxonase activity was carried out in the presence and absence of sodium chloride. The levels of paraoxonase without sodium chloride were calculated by adding 350 µl of a mixture consisting of paraoxon (2 mmol/l), calcium chloride (2 mmol/l) and Tris HCl buffer (pH 8.0) in 10 µl of serum. In the measurement of paraoxonase stimulating with sodium chloride, 1 mmol/l of sodium chloride was added to the above mixture. Phenyl acetate was used as substrate to determine arylesterase activity. Paraoxonase and arylesterase activities were measured by spectrophotometry at 405 and 270 nm, respectively [28].

ADA and XO

ADA activity was measured spectrophotometrically in serum, by the method of Giusti and Gakis [29]. The reaction was started by addition of the substrate (adenosine) to a final concentration of 21 mmol/l and incubations were carried out for 1 h at 37 C. The reaction was stopped by adding 106 mmol/l/0 16 mmol/l phenolnitroprusside/ ml solution. The reaction mixtures were immediately mixed to 125 mmol/l/11 mmol/lalkalinehypochlorite (sodium hypochlorite) and vortexed. Ammonium sulphate at a concentration of75µmol/l was used as ammonium standard. The ammonia concentration is directly proportional to the absorption of indophenol at 650 nm. The specific activity is reported as U/L in serum.

Results were expressed as units per liter of serum XO activity was measured spectrophotometrically by the formation of uric acid from xanthine through the increase in absorbance at 293 nm, according to Prajda and Weber's method [30].

NO

NO has very short half-life. The oxidation products of NO, nitrite (NO2-) and subsequently nitrate (NO-3), serve as an index of NO production. The method for measuring plasma nitrite and nitrate levels was based on the Griess reaction. Samples were initially deproteinized with Som/ogyi reagent. Total nitrite (nitrite+nitrate) was measured by spectrophotometry at 545 nm after conversion of nitrate to nitrite by copperized cadmium granule [20].A standard curve was established from nitrite standards to analyze unknown sample concentrations. Results were expressed as micromoles (µmol/L) [31].

Istatistic

All statistical analyses were carried out using SPSS statistical software. When the overall ANOVA revealed a significant effect, the data were further analyzed with the Tukey/Duncan post hoc test to determine specific group differences. Groups are considered significant when corresponding P values are < 0.05 or as determined by the Tukey/Duncan statistic after adjusting for multiple comparisons .P values less than 0.05 were considered to be signicificant. Statistical comparisons between groups were performed by Student's t test. All other data were expressed as mean ± s.d. Differences were considered statistically significant when P value was < 0.05 and are indicated in Table 1.

Results

The results are presented in Tables 2. The Paired Comparison of biomarkers in serum Between the Study Groups are presented in Table 3.In Group II, MDA, , PC levels and XO activity increased significantly compared to Group I.($p<0.05$).PS and Curcumin treatment ameliorated some enzyme levels (SOD, GSH-px, PON, ADA) in serum with phalloidin induced rats. Values of Group III approached Group I.

Table.2: SerumSOD ,GSH-Px, PON, ARE ,ADA ,XO activities and MDA, PC, and NO levels of all groups.									
Groups (n=7)	SOD (U/ml)	GSH-Px (U/l)	PON (mU/ml)	ARE (kU/l)	MDA (µmol/l)	PC (nmol/ml)	NO (µmol/l)	ADA (U/l)	XO (U/l)
G-I	12±1,0	70966, ±43	10,48±1,63	38,18±4,30	2,67±,39	254,1±21,1	31,6±2,2	295,5±21,4	0,7±0,12
G-II	7,79±0,76	662,5±30,17	7,73±1,32	30,20±2,67	3,91±0,531	309 ±8,02	35,05±4,24	255, ±29,1	1,07±,015
G-III	9,13±0,7	667,1±52,4	9,13±1,03	33,98±2,7	2,94±0,12	280,5±16,7	31,5±0,94	272±25,6	0,74±,1
G-IV	9,81,±0,49	690,5±9,9	9,59±0,9	35,7±2,1	2,82±0,21	268,0±31,9	32,75±2,48	294,8±15,4	0,66±,05
b-Abbreviations: **SOD**;Superoxide dismutase, **GSH-Px:**Glutathione peroxidase;**MDA:** Malonyldialdehyde , **NO :** Nitric oxide **ADA :** Adenosine Deaminase, **XO :**Xhanthine oxidase **PON:** Paraoxonase , **ARE :** Arylesterase GI : Contol, GII : Phalloidin , GIII: Phalloidin + PS , GIV : Phalloidin+ Curcumin									

Table 3 : The Paired Comparison of biomarkers in serum Between the Study Groups.						
P Values of Pair wise Comparisons						
	I vs. II	I vs. III	I vs. IV	II vs. III	II vs. IV	III vs. IV
SOD	0.001 *	0.001 *	0.001 *	0.01*	0.001 *	0.397**
GSH-Px	0.042*	0.,075**	0,657**	0,993**	0,335**	0,508**
PON	0.002*	0.221**	0.565*	0,195 **	0,05*	0.1**
ARE	0.00 *	0.076**	0.046*	0.012 *	0.013*	0.71**
MDA	0.002 *	0.694**	0.1**	0.026 *	0.01**	0.967*
NO	0,13**	0,08**	0,98**	0,1**	0,88**	0,83**
ADA	0,017*	0,267**	1,00**	,53**	,020*	,288**
XO	,006*	0,982**	0,969**	0,014*	0,002*	,084**
c-Abbreviations: **SOD**; Superoxide dismutase , ,**GSH-Px:** Glutathione peroxidase;**MDA:**Malonyldialdehyde , **NO :** Nitric oxide **ADA :** Adenosine Deaminase, **XO :**Xhanthine oxidase **PON:** Paraoxonase , **ARE :** Arylesterase * : signicifant **: Non-significant.						

Discussion

Phalloidin increases the level of ROS, Like other toxic substances (-amanitin,CCl_4,) [32-33]. Excessive levels of ROS can cause damage to cellular proteins, lipids, and nucleic acids, potentially having detrimental effects on function.Carbonyl groups can be introduced into proteins by oxidative reactions with oxygen-derived free radicals.Protein carbonyl levels as biomarker of oxidative stress [34]. They are lipids that are most affected by reactive oxygen species. Inasmuch as cell membranes are rich in polyunsaturated fatty acids (PUFAs) and cholesterol, they are easily affected by oxidant radicals. Lipid peroxidation; Where the unsaturated lipids are present, is a complex process that takes place with reactions involving molecular oxygen and is formed by lipid hydroperoxidesLipid peroxidation produces a wide variety of oxidation products, such as MDA is the oxidative stress biomarker.MDA levels were elevated in phalloidin-induced liver injury study [35-38].

In our study, PC and MDA levels increased in the group II .In groups III and IV, MDA and PC levels decreased in groups given PS and curcumin PS and Curcumin. Curcumin and PS have been observed to reduce MDA levels in many studies. Both antioxidant and detoxification properties have reduced free radicals in the environment [39-40-41]. Esterases play major roles in the hydrolysis of a number of prodrugs in humans and experimental animals [42]. PON plays a vital role in the *in vivo* detoxification of Organ phosphorus (OPs) and Serum PON is an enzyme which hydrolyses OPs, a reaction which is dependent onCa^{2+} ions [43-44]. ROS production is increased in mitochondria following the impairment of calcium balance. PON-1 and ARE play a role in decreasing oxidative stress. In Group I, PON and ARE activity is high while in Group II they are low. The reason for the low PON and ARE in Group II is the increased ROS and calcium imbalance. Phalloidin imparied calcium metabolism. Curcumin and PS increased Group III and Group IV PON and activity by reducing ROS in the environment [45]. ADA is considered one of the key enzymes of purine metabolism. Xanthine oxidase (XO) converts hypoxanthine and xanthine to uric acid by producing hydrogen peroxide (H_2O_2). XO produces large amounts of ROS [46-47].

In group II, ADA activity decreased while XO activity increased. Phalloidin may have disrupted the balance of purine metabolism. Impairment of purin metabolism and excessive production of ROS can initiate lethal radical chain reactions involving oxidation and damage of structures that are crucial for the integrity and survival of the cell. Group III and Group IV ADA and XO enzymes activities approached Group I. Curcumin and PS regulated purine metabolism.

Conclusion

Phalloidin increases toxic ROS. Increase of ROS causes oxidative stress.It has been observed that curcumin and PS reinforcement can inhibit oxidative stress formation. It is possible to remove toxic free radicals and prevent peroxidation reactions.Curcumin and PS are antitoxin.Curcumin and PS treatment in mushroom poisoning can be applied like silibin. However, clinical treatment and dose adjustment studies should be performed. Further research is needed to provide a deeper understanding of this topic.

Conflict of Interests

The authors declare that there are no commercial or associative interests that represent a conflict of interests in connection with the work submitted.

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