Effects of sophoroflavonoside and narcissin flavonoids on mitochondrial dysfunction and antioxidant enzyme activity in rat liver poisoned with galoxyfop-r-methyl pesticide

Mashxura Parpieva[1,*], *Parida* Mirkhamidova[2], *Mamurjon* Pozilov[3] and *Rano* Alimova[4]

[1]Andijan State University, Andijan, 170100, Uzbekistan
[2]Tashkent State Pedagogical University, Tashkent, 100070, Uzbekistan
[3]National University of Uzbekistan, Tashkent, 100174, Uzbekistan
[4]Tashkent State Agrarian University, Tashkent, 100140, Uzbekistan

Abstract. This study delves into the accumulation of residues in the liver tissue of rats exposed to the galoxyfop-R-methyl pesticide. The investigation also evaluates the presence of malondialdehyde (MDA), a lipid peroxidation (LPO) product, in the liver mitochondrial membrane, along with the activity of antioxidant enzymes catalase, superoxide dismutase (SOD), glutathione reductase (GR), and glutathione peroxidase (GP). The study further explores the impact of sophoraflavonoloside (SFL) and narcissin flavonoids on enzyme activity over a dynamic span of 10 to 40 days. In the experimental design, rats in the study group were subjected to galoxyfop-R-methyl pesticide at a dosage equivalent to LD50/10 through a specialized probe. Subsequently, the concentration of the pesticide residues in liver tissue was measured on the 5th, 10th, 20th, 30th, and 40th days post-pesticide exposure. The research also probes into the content of malondialdehyde (MDA) in the liver mitochondrial membrane, as well as the activity of antioxidant enzymes, within the context of SFL. This meticulous examination aids in comprehending the dynamics of enzyme responses and oxidative stress modulation in the liver of rats subjected to galoxyfop-R-methyl pesticide. By investigating the intricate interactions between pesticide exposure, enzyme activity, and antioxidant mechanisms, this study contributes to the broader understanding of the potential effects and counteractive measures concerning pesticide-related challenges in biological systems.
Keywords. Liver, mitochondria, galoxyfop–R–methyl (galoxyfop), SFL, narcissin, catalase, SOD, GR, GP.

1 Introduction

Pesticides, which are constantly used in agriculture today, lead to the development of metabolic diseases [1]. In case of acute and chronic poisoning with pesticides, damage to all

* Corresponding author: mashxura.parpieva1001@mail.ru

tissues, structural changes in bone marrow elements, peripheral blood, endocrine glands, liver, kidney, heart muscle and brain cells are observed [2, 3]. Pesticide poisoning affects all tissues and organs, but the most sensitive organ to their effects is the liver. Hepatocyte cells, which are actively involved in the metabolism of xenobiotics, become the main target of these pesticides. In the cell, mitochondria and microsomes are the most affected by pesticides. Taking into account the important role of these organoids, it is important to damage their membranes and thereby the cell and the organism as a whole [4]. Pesticides enter organs and tissues in various ways and accumulate as residues. Residual pesticide in the liver causes a number of functional changes, that is, it causes a change in the activity of LPO and enzymes [5]. But the slow elimination of pesticides from the liver reduces the activity of these enzymes. Residual pesticides can damage all systems of the human body and cause various pathological conditions [6]. The toxicity of some pesticides in mammals is manifested by the formation of free radicals and disturbance of redox balance [7].

Pesticides primarily damage liver tissue through the blood. The liver plays a key role in the detoxification process for xenobiotics. A change or violation of its function leads to hepatotoxicity and shows a significant increase in the activity of ALT, AST and alkaline phosphatase enzymes. These changes can affect membrane permeability and cause metabolite disturbances [8]. Metabolism of pesticides is explained by the disruption of the homeostatic mechanism of the cell by the production of reactive oxygen species (ROS). They interact with membrane lipids, disrupting the physiological balance between membrane lipids and proteins, especially mitochondrial substrate carriers and electron transporters [9].

A number of pesticides belonging to different classes cause increases in blood plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, lipids and inflammatory biomarkers [10]. According to the results of a study conducted with the herbicide galoxyfop-R-methyl, this herbicide causes oxidative stress in the liver and kidneys. This causes morphological, histopathological and immunological changes. The toxicity of galoxyfop-R-methyl in mammals has been determined to be related to the formation of CSF and disruption of redox activity in tissues [11]. The phytotoxicity of galoxyfop-R-methyl is based on the inhibition of the enzyme acetyl-CoA carboxylase [12].

Protection of the cell from LPO is carried out by a system of antioxidant enzymes. The most important protective enzymes are catalase, SOD, GR, GP, which neutralize the main and intermediate products of LPO, as well as secondary products of peroxidation of glutathione transferase, glyoxidase, formaldehyde dehydrogenases and other carbonyl compounds [13].

The purpose of the study is to determine the residual amount in the liver tissue of rats poisoned with galoxyfop-R-methyl and the corrective effect of SFL and narcissin flavonoids for 10, 20, 30 and 40 days on the content of the liver mitochondrial membrane LPO product MDA, the activity of antioxidant enzymes catalase, SOD, GR and GP is to determine the dynamics.

2 Materials and methods

Conducting scientific research on experimental animals was carried out on the basis of the international Declaration of Helsinki, the rules developed by the Council for International Organizations of Medical Sciences (CIOMS) (1985). Experimental animals were poisoned with 10.4% emulsion concentration of galoxyfop-R-methyl ($C_{16}H_{13}F_3ClNO_4$), a synthetic drug currently used in agriculture against weeds. The LD_{50} dose of galoxyfop-R-methyl in rats is 623 mg/kg. It is considered moderately toxic to humans and warm-blooded animals and has a level of toxicity of class 2 [14].

In our preliminary studies, indicators of residual amount of galoxyfop-R-methyl pesticide in liver tissue were determined. At the next stage of the study, healthy, experimental toxic

model (poisoned with a pesticide) and pharmacotherapy with flavonoids with antitoxic properties were conducted in vivo. galoxyfop-R-methyl pesticides were used to intoxicate animals. Each experimental group consisted of 3-5 animals.

Experimental animals were divided into separate model groups for intoxication with galoxyfop-R-methyl pesticide and their correction with flavonoids.

Initially, male rats selected for intoxication with galoxyfop-R-methyl pesticide were divided into groups:

Group I healthy (control) (n=5);

Group II galoxyfop-R-methyl (n=5-6);

Group III galoxyfop-R-methyl+SFL (n=5-6);

Group IV galoxyfop-R-methyl+ narcissin (n=5-6):

Animals in groups II, III and IV of the experiment were poisoned once with a dose of LD50 1/10 of galoxyfop-R-methyl pesticide through a special probe. After administration of galoxyfop-R-methyl pesticide, SFL 10 mg/kg of group III and narcissin flavonoid 10 mg/kg of animals were administered orally for 10 days.

The amount of residual pesticide in the liver tissue of rats poisoned with pesticides was determined after 5, 10, 20, 30, and 40 days, and after 10, 20, 30, and 40 days after administration of SFL and narcissin flavonoids to poisoned rats, the activity of mitochondrial antioxidant enzymes and the recovery of functional disorders of membranes were studied.

High-performance liquid chromatography mass spectrometry (6420 Triple Quad LC/MS (Agilent Technologies, USA) device was used for quantitative analysis of pesticides in liver samples. APCI (Atmospheric pressure chemical ionization) was used as the ionization method. performed at the expense of ionized ions.

Rat liver mitochondria were isolated using differential centrifugation W.C.Schneider [15] method.

The detection of LPO is based on the reaction between MDA and thiobarbituric acids (TBK), which results in the formation of a colored trimethine complex at high temperature and acidic pH [16]. The complex is measured in a spectrophotometer at a wavelength of 532 nm.

Determination of SOD enzyme activity (KF 1.15.1.1) Misra and J. Fridovich (1972). carried out according to the method [17]. Catalase activity in liver mitochondria Korolyuk M.A. determined using the method. Results are expressed in μKat/mg protein [18]. The activity of the GR enzyme was determined based on the accumulation of oxidized glutathione. Enzyme activity is expressed in micromoles of NADF.H per 1 g protein for 1 min at 370 C for 10 min at 340 nm wavelength (μM/min.g).

GP is determined by the accumulation of oxidized glutathione: occurs with the destruction of oxidized glutathione and is detected at a wavelength of 260 nm. Enzyme activity expresses glutathione in micromoles per 1 minute against 1 g of protein (μM/min.g). Mitochondrial protein was determined by Lowry's method.

3 Results and discussion

Galoxyfop-R-methyl pesticide was injected into the stomach of rats at a dose of LD_{50}1/10 through a special probe, and their residual amount in the liver of rats was determined on the 5th, 10th, 20th, 30th, and 40th days after poisoning. First, quantitative chromatographic analyzes were obtained from the livers of (healthy) galoxyfop-R-methyl and control animals. The average values obtained based on the characteristic absorption peaks for galoxyfop-R-methyl are shown in Table 1 below.

Table 1. Amount of residual pesticides in the liver of rats poisoned with galoxyfop -R-methyl (LD_{50}1/10).

Experimental groups	Residual amount of galoxyfop-R-methyl, 1 gram amount (mkg) relative to the sample (n=3).				
	Days				
	5	10	20	30	40
Control	-	-	-	-	-
Galoxyfop-R-methyl	0.01741	0.00159	0.000138	0.0000164	-

According to the obtained results, it was found that in the group of animals poisoned with galoxyfop-R-methyl pesticide, the amount of residual pesticides in the rat liver tissue was higher on the 5th and 10th days after poisoning than on the 20th and 30th days. On the 40th day, no residual amount of this pesticide was found. However, based on our results, it can be concluded that the amount of residual pesticides in the liver of rats can affect the biochemical and physiological indicators of liver mitochondria and cause a number of changes.

Intensity of the formation of CFS under the influence of pesticides causes an increase in LPO of the inner and outer membrane of mitochondria [3].

Pesticides weaken the antioxidant defense system in mitochondria, and antioxidant enzymes can degrade and reduce the amount of free radicals ($\bullet{}^1O_2$, $\bullet O_2^-$, •OH, and H_2O_2) in the cytosol.

For this purpose, in our present experiment, the effect of SFL and narcissin on the amount of LPO product MDA of rat liver mitochondria poisoned with pesticides was studied in relation to the dynamics of 10, 20, 30 and 40 days.

According to the obtained results, the amount of LPO product MDA in the membrane of liver mitochondria in group II rats poisoned with galoxyfop-R-methyl pesticide was 35.7±2.8%, 39 ,1±3.2%, 36.4±2.5% and 32.1±2.2% increase (Figure 1).

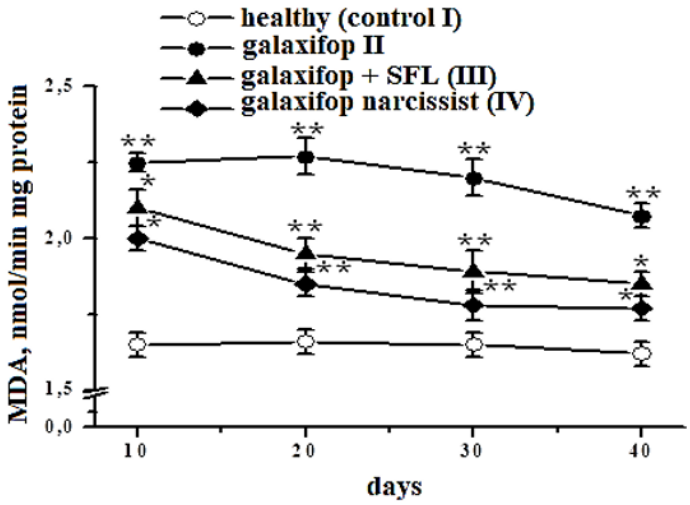

Figure 1. Dynamic effects of SFL and narcissine on MDA content of liver mitochondria of rats poisoned with the pesticide galoxyfop-R- methyl at 10, 20, 30 and 40 days (*R<0.05; *R<0.01; n=5-6).

This indicates the acceleration of the LPO process in the mitochondrial membrane under the influence of the galoxyfop-R-methyl pesticide. In group III rats pharmacotreated with SFL, the amount of liver mitochondria MDA was 9±0.8% on day 10, 15.6±1.2%, 21.3±1, and 21.3±1% on days 20, 30, and 40, respectively. 5% and 19.8±1.6% decrease (Figure 1).

After 10 and 20 days of narcissin-treated group IV rats, the MDA content was 11.5±0.9% and 21.6±1.6%, respectively, and a reliable decrease was observed compared to the values of group II. However, on days 30 and 40, it was found that the amount of MDA in liver mitochondria decreased by 28.6±2.1% and 26.0±2.2%, respectively, compared to the values of group II (Figure 1). It was found that the activity of narcissin was slightly higher than that of SFL on the amount of MDA in rat liver mitochondria poisoned with the pesticide galoxyfop-R-methyl.

Pesticides cause an increase in the level of LPO in liver mitochondria, and a decrease in the activity of SOD and catalase enzymes. It is known that the biological function of the enzymes of the antioxidant defense system is to protect cells from LPO products and other mutagenic effects.

Therefore, in our experiments, the dynamics of the corrective effect of SFL and narcissin flavonoids on the activity of liver mitochondria of rats poisoned with galoxyfop-R-methyl pesticide was studied for 10, 20, 30, 40 days. In our preliminary experiment, it was found that catalase activity decreased by 10, 20, 30 and 40 days in group II rats poisoned with galoxyfop-R-methyl pesticide compared to the control, and decreased by 45±3.2% in 40 days (Table 2).

Table 2. Effects of SFL and narcissin flavonoids on catalase enzyme activity of liver mitochondria of rats poisoned with the pesticide galoxyfop-R-methyl (10, 20, 30 and 40 days dependent dynamics) (μKat/mg protein).

Experimental groups	**n**	**Experience days**			
		10	**20**	**30**	**40**
Control	5	38.5±1.85	37.25±2.16	38.90±2.52	38.16±2.86
Galoxyfop-R-methyl	6	25.11±1.25*	24.35±1.21*	22.03±1.50*	20.95±1.04**
Galoxyfop-R-methyl +SFL	5	26.33±1.60	27.56±1.04*	28.71±1.43**	29.09±1.65**
Galoxyfop-R-methyl + Narcissin	5	26.57±1.90	28.11±1.40*	30.42±1.82**	33.95±2.27**

(*R<0.05; **R<0.01; n=5-6)

When group III rats treated with galoxyfop-R-methyl were treated with SFL flavonoid and group IV with narcissin, on days 10, 20, 30, and 40, their liver mitochondria catalase enzyme activity was 21±1.6% and 39±2%, respectively, compared to group II. It was found that it increased by 8% (Table 2).

Along with changes in catalase enzyme activity in liver mitochondria of rats poisoned with the pesticide galoxyfop-R-methyl, SOD activity also changes. SOD plays an important role in protecting cells and tissues from oxidative damage caused by negative factors. However, when SOD is activated, H_2O_2 is produced, which is an inhibitor of the enzyme. Therefore, the effective functional activity of SOD is mainly related to other components of the defense system, in particular, enzymes such as catalase, GR and GP. SOD inhibits the harmful reactions of superoxide by protecting the cell from superoxide toxicity [18]. Superoxide radicals are produced at two major sites in the electron transport chain, respiratory chain I (NADH dehydrogenase) and respiratory chain III (ubixinone cytochrome-c-reductase). As a result of the transfer of electrons from complex I or II to coenzyme Q or ubiquinone (Q), coenzyme Q (QH_2). the reduced form of is formed. The reduced form of

QH_2 regenerates coenzyme Q via an unstable anion (Q-) in the Q cycle. The created Q- immediately transfers electrons to molecular oxygen, leading to the formation of superoxide radicals. The formation of superoxide is not an enzymatic process, and therefore the higher the metabolic rate, the higher the production of ROS [17].

In our next experiment, the effect of SFL and narcissin flavonoids on the activity of liver mitochondria antioxidant enzyme SOD of rats poisoned with galoxyfop-R-methyl pesticide was investigated.

According to the obtained results, it was found that SOD activity decreased by 10, 20, 30 and 40 days in group II rats poisoned with galoxyfop-R-methyl pesticide, and on the 40th day, it decreased by 41.6±2.8% compared to the control. By day 40, the activity of SOD enzyme in liver mitochondria was 16.4 ± 1.2% and 22.7 ± 16.4 ± 1.2%, respectively, in rats treated with SFL flavonoid pharmacotherapy with SFL flavonoid and group IV treated with narcissin. An increase of 2.0% was shown in our experiments (Table 3).

Table 3. Effects of SFL and narcissin flavonoids on liver mitochondrial SOD enzyme activity (10, 20, 30, and 40-day dynamics) in rats poisoned with galoxyfop-R-methyl pesticide (ed/min.mg protein).

Experimental groups	n	Experience days			
		10	20	30	40
Control	5	3.30±0.06	3.28±0.06	3.26±0.05	3.34±0.06
Galoxyfop-R-methyl	6	2.57±0.06*	2.40±0.05*	2.23±0.05*	1.95±0.04**
Galoxyfop-R-methyl +SFL	5	2.36±0.05*	2.24±0.04*	2.30±0.09	2.44±0.05*
Galoxyfop-R-methyl + Narcissin	5	2.29±0.10*	2.20±0.06**	2.56±0.02**	2.71±0.03**

(*P<0,05; **P<0,01; n=5-6).

Activity of catalase and SOD enzymes, which are responsible for the antioxidant defense system, was observed to decrease in the experimental group, animals poisoned with pesticide. Decreased enzyme activity causes increased generation of free radicals in the mitochondrial respiratory chain. This, in turn, leads to the development of various pathological processes.

Thus, after 10-, 20-, 30- and 40-days after poisoning with galoxyfop-R-methyl pesticide, it was found that the activity of SOD and catalase enzymes of the antioxidant defense system of the liver mitochondria was sharply reduced. Selected plant flavonoids SFL and narcissin caused the activity of SOD and catalase enzymes to recover to a certain extent by the 30th and 40th days.

In addition to the changes in SOD and catalase activity in the liver mitochondria of rats poisoned with galoxyfop-R-methyl pesticide, the activity of GR and GP enzymes can also be changed. For this purpose, in our next experiment, the effect of SFL and narcissin on GR, GP enzymes, whose activity changed under the conditions of pesticide application, was studied.

Glutathione forms an antioxidant system in the cells of GP and GR. Glutathione not only protects cells from toxic effects such as free radicals, but also determines redox states in cells. In cells, the reduced form of thiol groups (SH) is present in a concentration of about 5 mM. Such a concentration of glutathione in the cell causes the restoration of disulfide (-S-S-) bonds formed between polypeptide chains of proteins [10].

The activity of antioxidant enzymes such as GR and GP in cell mitochondria can be significantly decreased under the influence of pesticides [8] In our next experiment, the effect of SFL and narcissin on the activity of mitochondrial antioxidant (GR, GP) enzymes in the liver mitochondria of rats poisoned with haloxyfop-R-methyl pesticide was studied in a 40-day dynamic state. .

Initially, in our experiments, under the influence of galoxyfop-R-methyl pesticide, changes in the activity of GR, one of the important antioxidant enzymes in liver

mitochondria, and the correcting properties of plant compounds were studied. According to the obtained results, it was found that GR activity in liver mitochondria of group II rats injected with galoxyfop-R-methyl herbicide at a single dose of LD_{50} 1/10 was significantly decreased compared to the control. It was found that under the influence of galoxyfop-R-methyl, the dynamics of changes in the activity of the liver mitochondrial GR enzyme showed the lowest value at 10 days and decreased by 38.1±2.5% compared to the control (Figure 2). It was found that the dynamics of GR activity under the influence of herbicides was reduced compared to the control even on the 20th, 30th and 40th days. However, there was no significant difference in GR activity compared to 10 days.

Group III rats treated with galoxyfop-R-methyl herbicide SFL and group IV animals were treated with narcissine at a dose of 10 mg/kg for 10 days. The liver mitochondria GR enzyme activity of group III rats corrected with SFL was pathological, i.e. 14.1±1.1%, 11.7±0.7%, 11.7±0.7%, respectively, on the 10th, 20th, 30th, and 40th day compared to the values of group II. It was found that it increased by 14.5±1.2% and 18±1.2% (Figure 2).

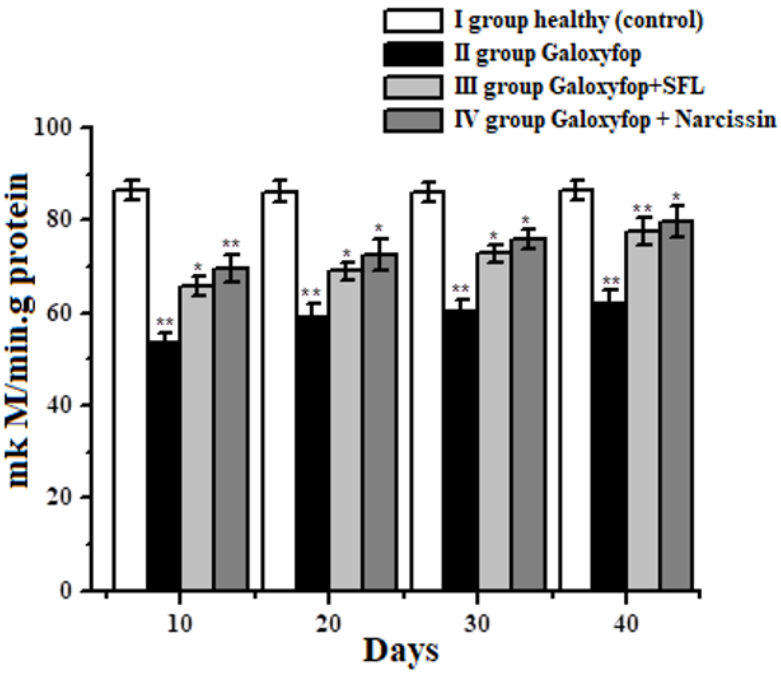

Figure 2. Effects of SFL and narcissin on glutathione reductase enzyme activity of liver mitochondria of rats poisoned with galoxyfop-R-methyl pesticide (*R<0.05; **R<0.01; n=5-6).

The liver mitochondria GR enzyme activity of group IV rats treated with narcissin was 18.4±1.1%, 15.8±1.3%, 18.0±1% compared to the pathological group on the 10th, 20th, 30th, and 40th days, respectively. It was noted that it increased by 1.2% and 20.3±1.9% (Figure 2). Therefore, depending on the dynamics, under the influence of SFL and narcissin, a certain degree of restoration of the activity of the liver mitochondrial GR enzyme was observed.

Along with other antioxidant enzymes, GP is one of the key enzymes in the catabolism of free radicals. GP enzyme acts to break down peroxidized lipids and H_2O_2 in mitochondria and cytoplasm to water and oxygen [8].

In mitochondria exposed to pesticides. In the literature, as a result of increased LPO process in rat erythrocyte cells under the influence of organochlorine pesticides, it was found that not only catalase, SOD, GR, but also GP activity decreased [15].

In our experiment, the 40-day effect of SFL and narcissin flavonoids on liver mitochondria GP activity of rats intoxicated with galoxyfop-R-methyl pesticide was studied in a dynamics-dependent manner. According to the obtained results, it was found that GP activity in liver mitochondria decreased sharply by 41±3.2% in group II compared to control (group I) by 10 days after administration of galoxyfop-R-methyl, and after 20 days, GP activity did not change much compared to 10 days. However, this indicator was observed to decrease by 27.5±2.1% and 28.5±1.3%, respectively, compared to the control by the 30th and 40th days (Figure 3).

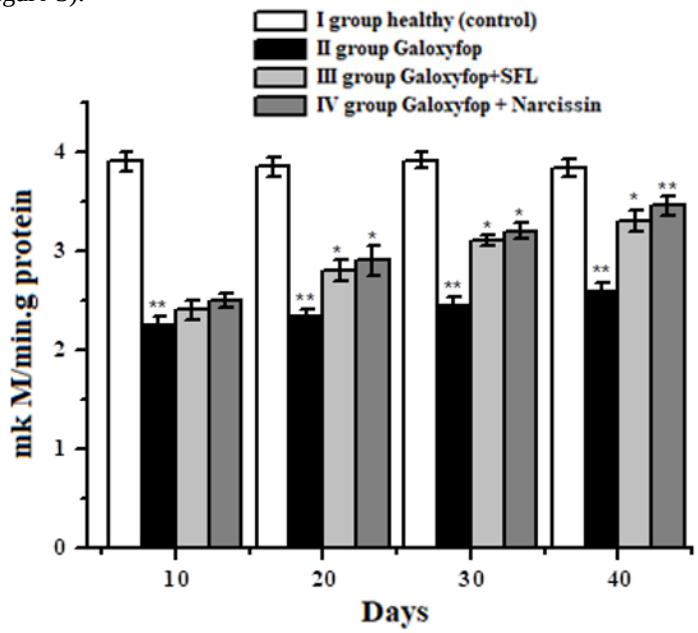

Figure 3. 40-day time-dependent effects of SFL and narcissine on glutathione peroxidase enzyme activity in liver mitochondria of rats poisoned with the pesticide galoxyfop-R-methyl. (*R<0.05; **R<0.01; n=5-6).

Group III rats intoxicated with galoxyfop-R-methyl were pharmacotreated with SFL orally for 10 days, and their GP activity in liver mitochondria did not change significantly compared to group II at 10 days, but by days 20, 30, and 40, 13 It was found that it increased by ±0.9%, 17±1.2% and 18.5±2.2%. Continuing the experiments in group IV rats poisoned with galoxyfop-R-methyl, and pharmacotherapy with narcissine for 10 days, the effect of this substance on GP activity was not noticeable at 10 days. However, on the 20th, 30th, and 40th days, it was found that it increased by 15.6±1.3%, 19.5±1.8%, and 22.3±1.2%, respectively (Figure 3). The results of the experiment showed that the effect of narcissine on GP activity in liver mitochondria was more effective than that of SFL.

4 Conclusions

Thus, in the liver mitochondria of rats poisoned with galoxyfop-R-methyl pesticide, an increase in the amount of LPO product MDA was observed on days 10-20, and a sharp decrease in the activity of catalase, SOD, GR, GP enzymes of the antioxidant defense system

was detected. In the SFL and narcissine-corrected groups, it was observed that the amount of LPO product MDA was restored to a certain extent and the activity of antioxidant enzymes was increased to a certain extent in the mitochondria of rat liver by 40 days.

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