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CORRECTION OF CYTOCHROME C RELEASE FROM THE INNER MITOCHONDRIAL MEMBRANE DURING LIPID PEROXIDATION IN ISCHEMIA USING GLABRANIN

Annotatsiya

Jigar mitoxondriyalarining ishemik shikastlanishi lipidlarning peroksidlanish jarayonlarining kuchayishi, oksidlovchi stress rivojlanishi va mitoxondriya membranalarining barqarorligini buzilishi bilan tavsiflanadi, bu esa oxir-oqibat gepatotsitlarning shikastlanishiga olib keladi. Malondialdegid (MDA) ning to‘planishi va sitoxrom c ning ajralib chiqishi ishemiya sharoitida mitoxondriyalar disfunksiyaning muhim ko‘rsatkichlari hisoblanadi. Ushbu tadqiqotda modellashtirilgan ishemiya sharoitida ajratib olingan kalamush jigar mitoxondriyalarida glabraninning lipid peroksidlanishi jarayonlari hamda mitoxondriyalarning membranalar barqarorligiga ta’siri baholandi. Mitoxondriyalar 36,7 °C haroratda autooksidlovchi stress bilan kechuvchi ishemik

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

sharoitda inkubatsiya qilindi. Lipid peroksidlanish darajasi MDA hosil bo‘lish dinamikasi orqali aniqlandi. Glabraninning himoya ta’siri uning MDA hosil bo‘lishiga hamda sitoxrom c ning ichki mitoxondriyalar membranadan ajralib chiqishiga ta’siri orqali baholandi. Olingan natijalar glabraninning ishemiya sharoitida kuchli antioksidant va mitoxondriyani himoyalovchi xususiyatlarga ega ekanligini tasdiqlaydi.

Kalit so‘zlar: Ishemiya, mitoxondriya, sitoxrom c, NADH-oksidaza, glabranin, oksidlovchi stress

Аннотация

Ишемическое повреждение митохондрий печени проявляется увеличением процессов перекисного окисления липидов, развитием окислительного стресса и нарушением целостности митохондриальных мембран, что в конечном итоге приводит к повреждению гепатоцитов. Ключевыми маркерами митохондриальной дисфункции при ишемии являются накопление малонового диальдегида (МДА) и высвобождение цитохрома с. В данном исследовании было изучено влияние глабранина на процессы перекисного окисления липидов и стабильность мембран митохондрий, изолированных из печени крыс в условиях моделируемой ишемии. Митохондрии инкубировались при температуре 36,7 °C в условиях ишемии с аутоокислительным стрессом. Уровень перекисного окисления липидов оценивался по динамике образования МДА. Защитные свойства глабранина анализировались на основе его влияния на уровень МДА и высвобождение цитохрома с из внутренней мембраны митохондрий. Полученные результаты указывают на выраженные антиоксидантные и защитные свойства глабранина в условиях ишемии.

Ключевые слова. Ишемия, митохондрия, перекисное окисление липидов, цитохрома с, НАДН-оксидаза, глабранин, оксидативный стресс

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

Abstract

Ischemic injury to liver mitochondria is strongly linked to increased lipid peroxidation, oxidative stress, and the destabilization of mitochondrial membranes, ultimately resulting in damage to hepatocytes. The accumulation of malondialdehyde (MDA) and the release of cytochrome care well-established markers of mitochondrial dysfunction in ischemic environments. This study focused on assessing the influence of glabranin on lipid peroxidation and the stability of mitochondrial membranes in isolated rat liver mitochondria subjected to induced ischemia. Mitochondria were isolated and incubated at a temperature of 36.7 °C under ischemic conditions marked by auto-oxidative stress. The intensity of lipid peroxidation was evaluated by tracking MDA formation over time. To intensify oxidative damage, a lipid peroxidation activator was introduced into the mitochondrial suspension. The protective effects of glabranin were analyzed through its impact on MDA production and cytochrome c release from the inner mitochondrial membrane. Ischemic incubation led to a gradual rise in MDA concentrations, indicating heightened lipid peroxidation, while the activator significantly expedited MDA accumulation and facilitated cytochrome c release. Treatment with glabranin resulted in a notable reduction in lipid peroxidation, lower levels of MDA, and inhibition of cytochrome c release, highlighting its stabilizing role on mitochondrial membranes. These results indicate that glabranin possesses potent antioxidant and protective properties for mitochondria during ischemic episodes.

Keywords. Ischemia, Mitochondria, lipid peroxidation; cytochrome c, NADH oxidase, glabranin, oxidative stress

Introduction

Mitochondria play a pivotal role in regulating cellular energy metabolism, maintaining redox balance, and controlling programmed cell death. Under normal physiological conditions, cytochrome c serves as a vital electron transporter

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

between complexes III and IV within the mitochondrial respiratory chain. However, during pathological events such as ischemia, cytochrome c takes on an additional function as a significant pro-apoptotic signaling molecule that triggers the activation of caspases, leading to cascades of cell death [1–3].

Ischemia is marked by insufficient oxygen supply, disruption of oxidative phosphorylation processes, accumulation of reduced electron carriers, and heightened production of reactive oxygen species (ROS). These factors contribute to oxidative stress-related damage to mitochondrial membranes, notably through lipid peroxidation. Such alterations severely impact membrane fluidity, protein-lipid interactions, and the efficiency of the respiratory chain [4–6]. Recent research indicates that lipid peroxidation linked to ischemia primarily affects cardiolipin—a phospholipid specifically located in the inner mitochondrial membrane that is critical for anchoring cytochrome c and facilitating electron transfer [7,8].

Historically, the release of cytochrome c has been associated with irreversible damage to mitochondria characterized by outer membrane rupture and the opening of the mitochondrial permeability transition pore (mPTP). Nonetheless, emerging evidence over the past five years suggests that cytochrome c can be released in a regulated manner without complete disruption of mitochondrial structural integrity or loss of bioenergetic function [9–11]. This regulated release appears to be closely related to cardiolipin oxidation, redox-dependent remodeling at mitochondrial contact sites, and changes in membrane permeability influenced by Bcl-2 family proteins [12,13].

A significant factor contributing to redox imbalance in mitochondria during ischemia is the activation of NADH-dependent oxidoreductases. In low-oxygen environments, enhanced activity of NADH oxidases leads to increased leakage of electrons from the respiratory chain. This results in elevated ROS production and accelerated lipid peroxidation processes [14,15]. Additionally, recent findings suggest a functional interplay between mitochondrial NADH oxidases and NADPH oxidase systems that creates a self-perpetuating redox loop exacerbating

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

damage to mitochondrial membranes while promoting the mobilization of cytochrome c [16].

Natural polyphenolic compounds have garnered substantial interest as potential protectors for mitochondria due to their antioxidant effects along with properties that stabilize membranes and inhibit apoptosis. Specifically, flavonoids have demonstrated effectiveness in reducing ROS generation, preventing lipid peroxidation, and safeguarding mitochondrial membrane integrity under conditions of ischemia and oxidative stress [17,18]. Among these compounds, glabranin has emerged as a promising bioactive agent capable of influencing mitochondrial redox status while protecting membrane phospholipids from oxidative harm.

Previous experimental research indicates that the auto-oxidation and lipid peroxidation caused by ischemia lead to significant disruptions in mitochondrial respiration and oxidative phosphorylation. These disturbances can be partially alleviated by natural flavonoids, such as glabranin [19].

Recent experimental studies suggest that polyphenols can inhibit cardiolipin oxidation. This action helps maintain cytochrome c's association with the inner mitochondrial membrane while restricting its pathological release into the cytosol [20]. Nevertheless, despite increasing interest in this area, there remains limited exploration into glabranin's specific impacts on mechanisms involved in cytochrome c release during lipid peroxidation induced by ischemia—particularly regarding its relationship with NADH oxidase activity and membrane stability.

The objective of this research was to explore how glabranin influences the release of cytochrome c during lipid peroxidation in mitochondria caused by ischemia. In accordance with the objectives set forth by the “Uzbekistan–2030” Development Strategy, this research sought to explore how glabranin influences the release of cytochrome c amid lipid peroxidation induced by ischemia in mitochondria. The findings aim to offer a deeper understanding of mitochondrial redox regulation and to bolster protective strategies that target mitochondria.

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

The current study offers a mechanistic perspective on how glabranin specifically influences both rotenone-sensitive and rotenone-insensitive NADH oxidase pathways, thereby affecting cytochrome c mobilization during lipid peroxidation induced by ischemia. This contrasts with earlier research that largely concentrated on the overall antioxidant properties of flavonoids.

Materials and methods. Male rats weighing 180-220 g were used in the experiments (vivarium of the Department of Pharmacology of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan, Tashkent) in accordance with the ethical rules for working with laboratory animals, as outlined in the "Regulations on the bioethics of the use of laboratory animals in scientific research" Institute of Biophysics and Biochemistry at the National University of Uzbekistan (protocol No. 3 of 01/11/2021). Rats were immobilized under light ether anesthesia, decapitated, and mitochondria were isolated from the liver according to the standard procedure. Mitochondria were separated from rat liver using differential centrifugation [21] in a solution containing 0.25 M sucrose, 10 mM Tris-HCl buffer (pH 7.4), and 2 mM EDTA. The isolated mitochondria were then washed twice and purified in an isolation buffer devoid of EDTA. Mitochondria were separated into two groups: the first served as the control, while the second had a lipid peroxidation activator.

Intact mitochondria allow us to investigate mostly the intensity of respiration and oxidative phosphorylation, which are dependent on the activity of mitochondrial respiratory chain enzymes to different degrees. However, intact mitochondria do not enable complete evaluation of these enzymes' overall activity, since the mitochondrial oxidative phosphorylation system is present but the access of oxidizing substrates to the enzymes' active sites is restricted.

The polarography technique was used to assess the influence of flavonoids on the activity of mitochondrial respiratory chain oxidase systems. It is well established that liver mitochondria have two oxidation pathways: the inner phosphorylating pathway during the oxidation of substrates and succinate by

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

NAD, and the external non-phosphorylating pathway during the addition of NADH. The initial component of this external respiratory chain is $NADH_2$-cytochrome b_5 reductase. Rotenone blocks one of these oxidation routes (the internal pathway). The measurement solution was made up of 0.05 M Tris-HCl (pH 7.4), 0.005 M histidine, and 0.66 M sucrose. In a 1-mL chamber, 3 μM NADH2 was utilized to measure the activity of rotenone-sensitive NADH oxidase. The activity of NADH oxidase was also assessed in the presence of 2 g of rotenone. The activities of rotenone-sensitive and rotenone-insensitive NADH oxidases were estimated using the total NADH oxidase activity [22]. The oxidase activity was described in nanograms of oxygen atoms consumed per minute per milligram of mitochondrial protein at 25°C. The reaction was begun by introducing mitochondria to the measuring medium in the chamber. The protein level in the mitochondrial samples was measured using the technique of Lowry et al. [23].

The results were analyzed statistically using OriginPro 6.0 software (Microsoft, USA). To assess the differences between the control and experimental groups, Student's t-test was applied, with a P value of less than 0.05 deemed statistically significant.

Results and discussion. Alterations in NADH oxidase activities during ischemia. The impact of ischemia-related lipid peroxidation on mitochondrial respiratory functions is detailed in Table 2. In conditions of auto-oxidation, the activity of rotenone-sensitive NADH oxidase (which indicates inner mitochondrial respiration) showed a biphasic pattern. After incubation periods of 3 and 6 minutes, enzyme activity rose by 7.9% and 29.5%, respectively, approaching or slightly surpassing control levels. This brief increase may reflect a compensatory mechanism aimed at sustaining electron transport during initial ischemic stress.

Conversely, extended incubation times (ranging from 9 to 15 minutes) led to a notable reduction in rotenone-sensitive NADH oxidase activity, with up to a

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

31.1% decrease compared to controls. This decline is associated with heightened lipid peroxidation and points towards a progressive deterioration of the inner mitochondrial membrane as well as components of the respiratory chain. In contrast, the activity of rotenone-insensitive NADH oxidase (indicative of outer respiration) demonstrated a consistent and gradual increase throughout the ischemic incubation period. While only minor fluctuations were noted at the 3-minute mark, activity surged by 18.4%, 35.5%, and 43.0% after 6, 9, and 15 minutes, respectively. This progression signifies increased electron leakage and redox imbalance, which aligns with damage-induced alterations in mitochondrial membranes.

Table 2. **Changes in the activity of rotenone-sensitive and rotenone insensitive NADH oxidase in mitochondria during autooxidation and lipid peroxidation under ischemic conditions. (M ± m; n = 10-12)**

Parameter	Time, minutes	Respiration rate, ng-atom O_2 / min·mg protein			
		AO	%	LPO	%
Rotenone-sensitive NADH oxidase	0	51,61±5,12	100	51,61±5,12	100
	3	55,69±5,18	107,9	65,28±5,08	126,5
	6	66,83±5,79	129,5	59,25±4,52***	114,8
	9	49,80±6,66***	96,5	45,36±5,32***	87,9
	15	30,40±5,30****	68,9	22,40±3,60****	43,4
Rotenone-insensitive NADH oxidase	0	5,14±0,38	100	5,14±0,38	100
	3	5,37±0,33	104,5	6,11±0,37	118,9
	6	6,08±0,33	118,4	6,82±0,45	132,8
	9	6,96±0,39**	135,5	7,86±0,40****	152,9
	15	7,35±0,50****	143,0	8,67±0,37****	168,7

As a result, the rotenone-sensitive NADH oxidase activity begins to rise slowly after three minutes of mitochondrial incubation under ischemic conditions (autooxidation), reaches its peak around six minutes, approaches control values by

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

the ninth minute, and subsequently falls by the fifteenth minute. In contrast, the activity of the rotenone-insensitive NADH oxidase gradually rises from the start, and this process accelerates as the experiment progresses. When mitochondria are incubated with a lipid peroxidation activator, NADH oxidase activity peaks after 3 minutes and then gradually drops. At the same time, rotenone-insensitive NADH oxidase activity increases from the start of incubation and accelerates throughout the experiment.

According to an analysis of the collected data, the production of cytochrome c from the inner mitochondrial membrane into the intermembrane space during auto oxidation under ischemic circumstances is initially modest, but grows more prominent as incubation progresses. The release of cytochrome c is considerably increased when mitochondria are incubated in the presence of a lipid peroxidation inducer.

Cytochrome c mobilization and membrane destabilization. The reciprocal alterations observed in both rotenone-sensitive and rotenone-insensitive NADH oxidase activities serve as indirect yet strong evidence for the release of cytochrome c from the inner mitochondrial membrane into the intermembrane space. In the initial stages of ischemia, the dissociation of cytochrome c appears to be limited, indicating that respiratory functions are still maintained. However, as lipid peroxidation progresses, it leads to cardiolipin oxidation and destabilization of the membrane, which promotes the movement of cytochrome c. This mobilization results in disrupted electron transfer and increased outer respiratory activity.

Protective effects of glabranin on mitochondrial respiration. Importantly, the introduction of lipid peroxidation inducers significantly accelerates this process, reinforcing the idea that oxidative modifications to mitochondrial phospholipids play a crucial role in triggering cytochrome c release during ischemic episodes.The effects of lipid peroxidation during ischemia on the activity

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

of rotenone-sensitive and rotenone-insensitive NADH oxidases. When mitochondria were incubated for 3 and 6 minutes under lipid peroxidation conditions, the activity of the rotenone-sensitive NADH oxidase increased by 26.5% and 14.8%, respectively, compared to the control; however, at the ninth minute, activity dropped by 12.1%, and this decline accelerated to 66.6% by the 15th minute. Meanwhile, the activity of rotenone-insensitive NADH oxidase increased by 8.9%, 26.8%, 42.9%, and 58.7% at 3, 6, 9, and 15 minutes of the experiment, respectively.When lipid peroxidation was deliberately triggered, notable alterations in NADH oxidase activities were observed. The activity of rotenone-sensitive NADH oxidase reached its maximum at 3 minutes (+26.5%) but subsequently experienced a sharp decline, resulting in a significant decrease of 56.6% by the 15-minute mark. In contrast, the activity of rotenone-insensitive NADH oxidase exhibited a continuous and steeper increase compared to auto-oxidation, culminating in a rise of 68.7% at the final measurement point.

These findings illustrate that lipid peroxidation severely influences mitochondrial respiratory equilibrium, leading to a transition from energy-efficient respiration to non-coupled pathways that generate reactive oxygen species (ROS).

When glabranin was introduced to mitochondria, the activity of rotenone-sensitive NADH oxidase decreased slightly at 3 and 6 minutes of incubation, increasing by just 12.5% and 10.4% relative to the control, respectively. This statistic achieved the control level by the 9th minute, but then fell by the 15th minute, indicating just a 24.1% rise above the control. The activity of the rotenone-insensitive NADH oxidase did not change in the third minute, but began to rise in the sixth minute, and this process accelerated as the experiment progressed. If the increase was 12.8% at the 6th minute, it accelerated to 22.5% and 34.9% at the 9th and 15th minutes, respectively.

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

As a result, glabrannin dramatically slows the initial increase and subsequent decrease in the activity of the rotenone-sensitive NADH oxidase during mitochondrial lipid peroxidation in ischemic conditions. It also slows the pace of increase in rotenone-insensitive NADH oxidase activity. As a result, glabrannin reduces the creation of "monolayer" flaws in the mitochondrial membrane during ischemia, stabilizes the membrane, and inhibits the action of endogenous lytic enzymes.

Mechanistic implications. The data collectively indicate that lipid peroxidation caused by ischemia results in a gradual destabilization of the mitochondrial membrane, an increase in cytochrome c release, and a disruption of respiratory control. Glabranin mitigates these consequences by decelerating lipid peroxidation, safeguarding the interactions between cardiolipin and cytochrome c, and inhibiting the development of membrane defects that contribute to electron leakage and enzymatic lysis. These mechanistic relationships are summarized in a schematic model illustrating ischemia-induced lipid peroxidation, cytochrome c release, and their correction by glabranin (**Figure 1**).

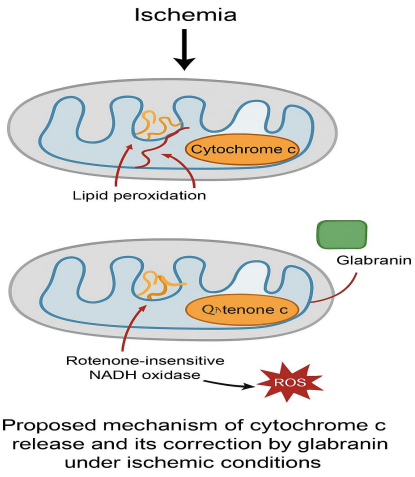


Figure 1. Proposed mechanism of cytochrome c release and its correction by glabranin under ischemic conditions.

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

Ischemia leads to an imbalance in mitochondrial redox status, triggers lipid peroxidation of the inner mitochondrial membrane, interferes with the interactions between cardiolipin and cytochrome c, and increases the activity of NADH oxidase that is not sensitive to rotenone. This cascade results in heightened production of reactive oxygen species (ROS) and the release of cytochrome c. Conversely, glabranin plays a protective role by stabilizing membrane phospholipids, inhibiting lipid peroxidation, normalizing NADH oxidase activity, and preventing the abnormal release of cytochrome c.

Our research aligns with recent studies indicating that lipid peroxidation caused by ischemia significantly contributes to the destabilization of the inner mitochondrial membrane and the release of cytochrome c [24, 25]. In a similar vein, Li et al. [27] reported that excessive production of mitochondrial reactive oxygen species (ROS) and oxidation of cardiolipin promote cytochrome c dissociation from the inner mitochondrial membrane without leading to immediate rupture of the mitochondria. Furthermore, investigations by Murphy and Hartley [26] highlighted that redox-dependent alterations in mitochondrial membranes are critical during episodes of ischemic stress.

In contrast to these previous works, which primarily examined overall oxidative damage and apoptosis signaling pathways, our study offers a more nuanced analysis of how rotenone-sensitive and rotenone-insensitive NADH oxidase activities are differentially regulated under ischemic conditions. Our findings indicate that ischemia first enhances the activity of rotenone-sensitive NADH oxidase, followed by a significant decrease, while there is a gradual increase in rotenone-insensitive NADH oxidase activity. This suggests a shift towards alternative pathways for electron leakage and ongoing ROS production [28, 29].

This variation may stem from differences in the experimental models used as well as variations in endogenous lipid peroxidation systems. Notably, our results

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

demonstrate that glabranin effectively influences both NADH oxidase pathways, reduces lipid peroxidation, preserves mitochondrial membrane integrity, and restricts detrimental cytochrome c release. These outcomes build upon earlier findings regarding flavonoid-mediated mitochondrial protection [30, 31], positioning glabranin as a specific regulator of mitochondrial dysfunction induced by ischemia.

Consequently, glabranin functions as a protector of the mitochondrial membrane, diminishing oxidative damage and preserving bioenergetic stability during ischemic conditions.

Conclusion. In summary, ischemic conditions observed in mitochondrial preparations lead to a gradual increase in oxidative activities, which is evident through heightened lipid peroxidation and notable disruptions in the equilibrium between rotenone-sensitive and rotenone-insensitive NADH oxidase activities. Both spontaneous autooxidation and induced lipid peroxidation play roles in destabilizing membranes over time, thereby exacerbating oxidative damage to mitochondrial structures. The use of glabranin has been shown to effectively reduce these changes by maintaining mitochondrial membrane integrity, decreasing lipid peroxidation, and stabilizing the function of NADH oxidase. By minimizing the development of membrane defect zones and curbing excessive oxidative processes, glabranin may hinder the activation of endogenous lytic enzymes during ischemic events. Overall, these findings underscore the protective effect of glabranin in sustaining mitochondrial redox homeostasis and alleviating oxidative injury caused by ischemia.

These results suggest that glabranin may serve as a valuable modulator targeting mitochondria, with possible significance for liver conditions associated with ischemia.

https://wordlyknowledge.uz/index.php/gpble
Qabul qilingan sana: 07.12.2025
Nashr etilgan sana: 30.01.2026

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