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Article

Experimental Evaluation of the Antihypoxic and Antioxidant Activity of the Phytocomposition "Glizimed" in Models of Hypobaric and Hemic Hypoxia

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Abstract: This study was conducted to evaluate the antihypoxic and antioxidant effects of the phytocomposition "Glizimed", prepared from medicinal plants, in experimental models of hypobaric and hemic hypoxia in mice, and to identify possible pathogenetic mechanisms underlying its protective action. Experimental studies were carried out in the vivarium of the Department of Sanitary and Epidemiological Control, Main Medical Directorate, under the Administration of the President of the Republic of Uzbekistan. The experiments involved male albino mice weighing 18–24 g, divided into control and treatment groups. Glizimed was administered intragastrically at doses of 10, 25, and 50 mg/kg. Piracetam (100 mg/kg) and Phytin (200 mg/kg) served as reference drugs. Hypobaric hypoxia was induced by simulating ascent to an altitude of 11,000 m, while hemic hypoxia was modeled by subcutaneous sodium nitrite administration (200 mg/kg). Survival time was recorded as the criterion of antihypoxic activity. Administration of Glizimed significantly increased the lifespan of mice compared with control: by 140.4% under hypobaric hypoxia and by 141.1% under hemic hypoxia. The phytocomposition exhibited superior efficacy compared to Piracetam and Phytin, especially at 25 mg/kg. Glizimed demonstrates pronounced antihypoxic and antioxidant properties in experimental hypoxia, suggesting potential use as a natural pharmacological protector against oxygen deficiency.

Keywords: *Glizimed, hypoxia, phytocomposition, antihypoxic activity, antioxidant, hypobaric hypoxia, hemic hypoxia, laboratory animals.*

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1. Introduction

The human body is constantly exposed to various environmental factors, among which hypoxia oxygen deficiency is one of the most widespread and pathologically significant [1], [2]. Sudden oxygen deficiency can lead to severe complications and even death; therefore, pharmacological protection of the organism from hypoxia remains an urgent problem in modern medicine [3], [4]. Hypoxia, regardless of its etiology, results in impaired oxidative metabolism and energy deficiency, leading to multiple organ dysfunction and, in severe cases, death. Despite the availability of synthetic drugs with antihypoxic properties, many of them exhibit limited efficacy and potential side effects [5]. Therefore, the search for new natural compounds with antihypoxic and antioxidant activities remains an important area of modern pharmacology [6].

Herbal preparations have long been recognized as a source of biologically active substances that enhance tissue oxygen utilization, improve cellular metabolism, and

mitigate oxidative stress [7], [8]. In this regard, we developed a phytocomposition named Glizimed, containing extracts of Hypericum perforatum (St. John's wort), Achillea millefolium (yarrow), Plantago major (plantain), and Glycyrrhiza glabra (licorice root). These plants are known for their antioxidant, adaptogenic, and membrane-stabilizing effects.

The present study aimed to experimentally evaluate the antihypoxic and antioxidant effects of the phytocomposition Glizimed in models of hypobaric and hemic hypoxia, and to compare its efficacy with known reference agents Piracetam and Phytin.

Based on the known pharmacological properties of the selected medicinal plants, we hypothesize that the phytocomposition *Glizimed* exhibits its antihypoxic and antioxidant activities through a complex synergistic mechanism. The active phytoconstituents flavonoids, phenolic acids, and saponins are likely to stabilize mitochondrial oxidative phosphorylation by maintaining the activity of respiratory chain enzymes and preventing the dissipation of the mitochondrial membrane potential. This effect helps preserve adenosine triphosphate (ATP) synthesis under oxygen-deficient conditions, thereby supporting cellular energy homeostasis.

Moreover, *Glizimed* is expected to activate endogenous antioxidant defense systems, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, which play a crucial role in scavenging reactive oxygen species (ROS) generated during hypoxia and reperfusion. By reducing lipid peroxidation processes, the phytocomposition protects phospholipid components of biological membranes from oxidative degradation, leading to improved membrane stability and ion transport regulation.

In addition, certain bioactive compounds of *Hypericum perforatum* and *Glycyrrhiza glabra* are known to modulate intracellular calcium balance and nitric oxide synthesis, which may contribute to better microcirculatory adaptation and oxygen utilization in hypoxic tissues. Collectively, these synergistic interactions are presumed to enhance mitochondrial efficiency, reduce oxidative stress, and increase overall tissue tolerance to oxygen deprivation [9], [10], [11].

2. Materials and Methods

Experimental design. All experiments were conducted on clinically healthy, male albino mice weighing 18–24 g. Animals were housed in standard plastic cages (6–8 animals per cage) under controlled conditions (temperature 20–25°C, humidity ≥50%, natural light/dark cycle) with free access to food and water. The mice were acclimatized for at least two weeks before the experiment (Table 1).

Table 1. Experimental grouping and treatment of animals

Group No.	Experimental group	Administered substance	Administered substance	Route administration	Number of animals (n)
1.	Control	Distilled water	-	Intragastric	8
2.	Glizimed (Low dose)	Glizimed	10 mg/kg	Intragastric	8
3.	Glizimed (Medium dose)	Glizimed	25 mg/kg	Intragastric	8
4.	Glizimed (High dose)	Glizimed	50 mg/kg	Intragastric	8
5.	Reference drug 1	Piracetam	100 mg/kg	Intragastric	8
6.	Reference drug 2	Phytin	200 mg/kg	Intragastric	8

Table 1 Summarizes the grouping and treatment of animals. All substances were administered intragastrically using a metal-tipped syringe (with a blunt needle) 24 hours and 1 hour before induction of hypoxia.

Preliminary phytochemical screening of the individual plant extracts included in the *Glizimed* phytocomposition was carried out according to standard pharmacognostic procedures [12]. Qualitative analysis revealed the presence of flavonoids, phenolic compounds, tannins, saponins, glycosides, and essential oils, which are known to contribute to antioxidant, membrane-stabilizing, and anti-inflammatory effects.

The total flavonoid and phenolic content were determined spectrophotometrically using aluminum chloride and Folin–Ciocalteu methods, respectively. The analysis confirmed that *Glizimed* possesses a high concentration of polyphenolic compounds—mainly rutin, quercetin, and glycyrrhizic acid derivatives—that are responsible for its pronounced antioxidant and antihypoxic activity.

Induction of hypoxia. Hypobaric hypoxia was modeled using a decompression chamber simulating ascent to 11,000 meters at a rate of 1,000 m/min, maintaining reduced barometric pressure and sufficient airflow [13]. Hemic hypoxia was induced by subcutaneous administration of sodium nitrite (200 mg/kg), which converts hemoglobin into methemoglobin, reducing oxygen transport capacity [14].

Criterion of efficacy. The main criterion of antihypoxic activity was survival time (in seconds) from the induction of hypoxia until the appearance of the second agonal breath.
Statistical analysis. Data were expressed as mean ± standard error of mean (SEM). Statistical significance was evaluated using Student's t-test, with $p < 0.05$ considered significant.

Ethical approval. All procedures complied with the principles of humane treatment of laboratory animals and were approved by the Institutional Animal Ethics Committee of Urgench State Medical Institute (Protocol No. 02/2024).

3. Results

Experimental results (Figure 1) demonstrated that the phytocomposition Glizimed significantly increased the survival time of animals under both hypobaric and hemic hypoxia compared with the control group. Under hypobaric hypoxia, Glizimed at 10 mg/kg prolonged the survival time by 26.9%, at 25 mg/kg by 140.4%, and at 50 mg/kg by 129.8%. Piracetam and Phytin increased the lifespan by 123.8% and 128.1%, respectively.Thus, the antihypoxic effect of Glizimed, particularly at 25 mg/kg, was slightly higher than that of the reference drugs. This marked increase in hypoxia resistance indicates that Glizimed effectively enhances cellular adaptation mechanisms to oxygen deficiency.

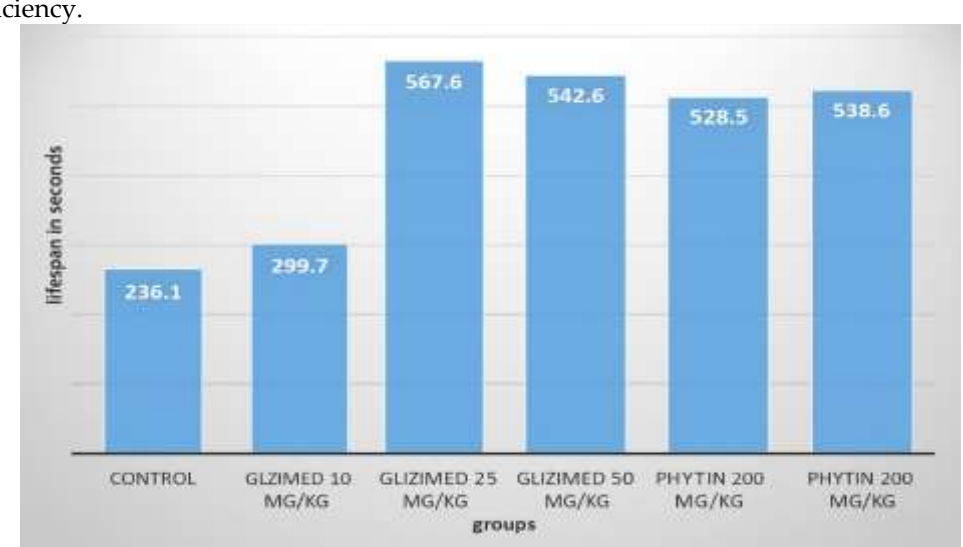

Figure 1. Survival time of mice under hypobaric hypoxia after administration of Glizimed, Piracetam, and Phytin.

The superior efficacy of the 25 mg/kg dose suggests an optimal concentration at which the synergistic phytochemical interactions particularly of flavonoids, saponins, and phenolic compounds contribute maximally to the stabilization of mitochondrial oxidative phosphorylation, activation of endogenous antioxidant enzymes (SOD, catalase), and suppression of lipid peroxidation. These findings are consistent with previous research demonstrating that phytocompositions containing polyphenolic constituents improve bioenergetic efficiency and oxidative stability under hypoxic stress conditions [9], [12], [15], [16]. Therefore, the obtained data confirm that Glizimed possesses potent antihypoxic and antioxidant properties, supporting its potential use as natural pharmacological protector against oxygen deficiency.

Experimental results (Figure 2) show that under hemic hypoxia induced by parenteral administration of sodium nitrite, the survival time of control rats ranged from 420.0 to 720.0 seconds, with an average of 560.0 ± 44.1 seconds. Pretreatment with Piracetam and Phytin increased the survival time by 2.1 and 2.2 times, respectively. Glizimed showed a dose-dependent and superior effect: 10 mg/kg increased survival by 37.5%, 25 mg/kg by 141.1% (2.4 times), and 50 mg/kg by 133.9%. These results indicate that Glizimed possesses a pronounced antihypoxic activity in both hypoxia models, with maximal efficacy at 25 mg/kg.

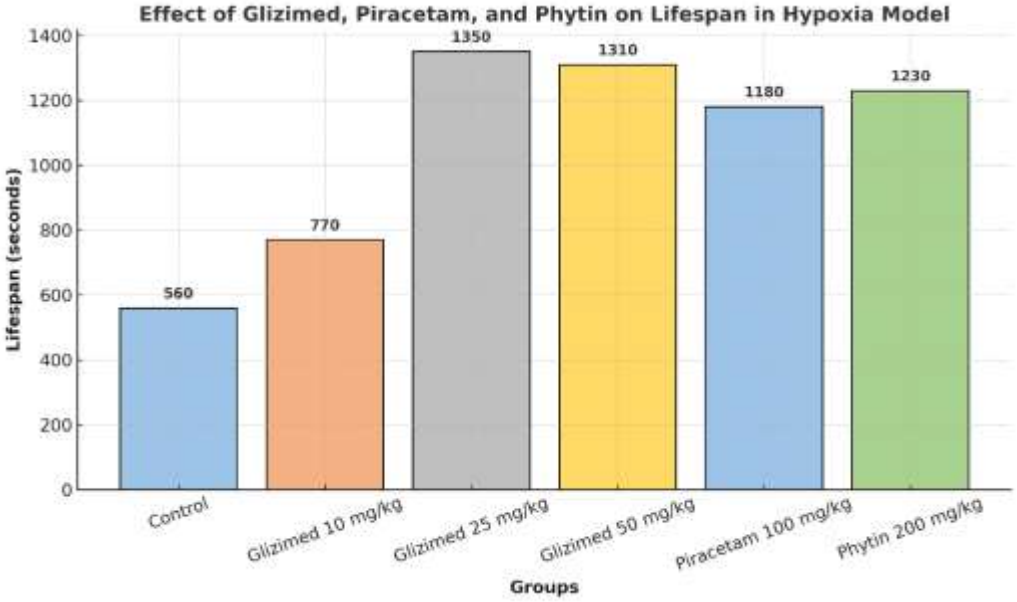

Figure 2. Survival time of mice under hemic hypoxia (sodium nitrite model) after pretreatment with Glizimed, Piracetam, and Phytin.

4. Discussion

The experimental results confirm that Glizimed exhibits potent antihypoxic and antioxidant properties in conditions of oxygen deficiency. The observed increase in survival time suggests that Glizimed enhances cellular tolerance to hypoxia by improving energy metabolism and protecting biological membranes from oxidative damage.

The efficacy of Glizimed was comparable to, and in some cases exceeded, that of the reference agents Piracetam and Phytin. This may be attributed to the synergistic effects of its components: Hypericum perforatum contains flavonoids and hypericin, which stabilize mitochondrial respiration and reduce lipid peroxidation. Achillea millefolium and Plantago major improve microcirculation and capillary permeability, facilitating oxygen delivery. Glycyrrhiza glabra possesses antioxidant and anti-inflammatory properties that enhance cellular defense mechanisms.

These pharmacodynamic properties are consistent with previous reports that emphasize the antioxidant and cytoprotective roles of polyphenolic compounds in maintaining mitochondrial function during hypoxia [15].

Our findings suggest that Glizimed's activity is likely mediated by the stimulation of aerobic glycolysis, activation of enzymatic antioxidant systems (superoxide dismutase, catalase), and stabilization of intracellular calcium balance mechanisms commonly involved in antihypoxic protection [16].

Thus, Glizimed can be considered a promising plant-derived antihypoxic and antioxidant agent, suitable for further pharmacological and clinical evaluation.

5. Conclusion

The phytocomposition Glizimed, composed of extracts from Hypericum perforatum, Achillea millefolium, Plantago major, and Glycyrrhiza glabra, exhibits strong antihypoxic and antioxidant activity in models of both hypobaric and hemic hypoxia. At a dose of 25 mg/kg, Glizimed significantly prolonged animal survival and demonstrated higher efficacy compared with the known agents Piracetam and Phytin. These results highlight the potential of Glizimed as a natural pharmacological protector against oxygen deficiency and oxidative stress, warranting further biochemical and clinical research.

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