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REVIEW ARTICLE

Plant derived and synthetical antihypoxic agents in cardiovascular diseases: Mechanisms, key pathways and therapeutic potential

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Abstract

Antihypoxic drugs are vital for protecting cells from oxygen deprivation in ischemia, stroke and heart failure. Despite their clinical potential, a unified understanding of their mechanisms and optimization strategies remains limited. This review addresses this gap by exploring how these agents interact with mitochondrial and cardiovascular ion channels to preserve cellular viability under hypoxic stress. We focus on their modulation of mitochondrial permeability transition pores (mPTP), ATP-sensitive potassium (K-ATP) channels and calcium flux through L-type and R-type channels, which are central to maintaining mitochondrial integrity and vascular function. Additionally, we examine how these compounds regulate hypoxia-inducible factor 1-alpha (HIF-1α), promote efficient electron transport and sustain redox homeostasis. Key strategies for enhancing therapeutic efficacy such as increasing lipophilicity, introducing conjugated π-systems and modifying functional groups are discussed in relation to membrane permeability and intracellular delivery. Particular emphasis is placed on the physicochemical properties that influence bilayer penetration and target specificity. Overall, this review highlights the structural and functional features that underlie the effectiveness of antihypoxic agents and provides insight into their optimization for improved clinical performance in hypoxia-related pathologies.

Keywords: cardiovascular pharmacology; mitochondrial diseases; pharmacology; vascular disease

Introduction

Hypoxia, a condition characterized by inadequate oxygen supply to tissues, plays a crucial role in various physiological and pathological processes. It can arise due to reduced oxygen availability in the environment or because of impaired oxygen delivery to tissues, such as in cardiovascular diseases. The heart and brain, which are highly dependent on a constant supply of oxygen, are particularly vulnerable to hypoxic stress. In the cardiovascular system, prolonged or severe hypoxia leads to metabolic disturbances, impaired energy production, oxidative stress and ultimately, cell death. This process is a key factor in the development of ischemic conditions, including myocardial infarction, stroke and heart failure, where the lack of oxygen impairs normal cellular function and disrupts the delicate balance of homeostasis (1, 2).

The body's natural response to hypoxia involves various adaptive mechanisms, such as the activation of Hypoxia-Inducible Factor-1 (HIF-1), which regulates genes involved in oxygen homeostasis, angiogenesis and metabolic reprogramming. However, in severe or prolonged hypoxic states, these adaptive responses may be insufficient to prevent irreversible tissue damage. In such cases, pharmacological interventions, specifically antihypoxic drugs, play a critical role in restoring cellular oxygen balance, preventing hypoxia-induced damage and improving survival outcomes (3, 4).

Antihypoxic drugs have garnered significant clinical interest due to their potential to mitigate the effects of oxygen deprivation in diseases such as ischemia, stroke, chronic obstructive pulmonary disease (COPD) and heart failure. These drugs work through various mechanisms, including enhancing oxygen delivery, protecting mitochondrial function, stabilizing HIF-1 and modulating redox balance. The development of these therapies not only offers new avenues for treating hypoxia-related diseases but also provides insights into their underlying molecular mechanisms, enabling more targeted and effective interventions (5). In this review, we will explore the molecular mechanisms of antihypoxic drugs, their adaptive properties and the potential therapeutic pathways through which they exert their protective effects in hypoxic conditions (6).

Classification of antihypoxic drugs

Antihypoxic drugs can be classified into several categories based on their mechanisms of action and chemical structures.

Each group targets specific molecular pathways and cellular mechanisms to mitigate the effects of hypoxia (Fig. 1).

Based on mechanism of action

Mitochondrial protection agents: These drugs help protect mitochondria from oxidative damage and maintain ATP production during hypoxia (7, 8). Mitochondrial dysfunction is a primary consequence of hypoxia, leading to increased reactive oxygen species (ROS) production and impaired energy generation. Examples: Coenzyme Q10, L-carnitine, cytochrome C, mitoK-ATP channel modulators (9, 10) (Fig. 2).

HIF-1 stabilizers (HIF-1): These drugs act by stabilizing the HIF-1 protein, which is crucial for the cellular adaptation to low oxygen levels (11, 12). By enhancing HIF-1 activity, these agents promote angiogenesis, erythropoiesis and metabolic reprogramming, enabling cells to survive under hypoxic conditions (13, 14). Examples: Roxadustat, desidustat, molidustat (HIF-PHD inhibitors) (Fig. 3).

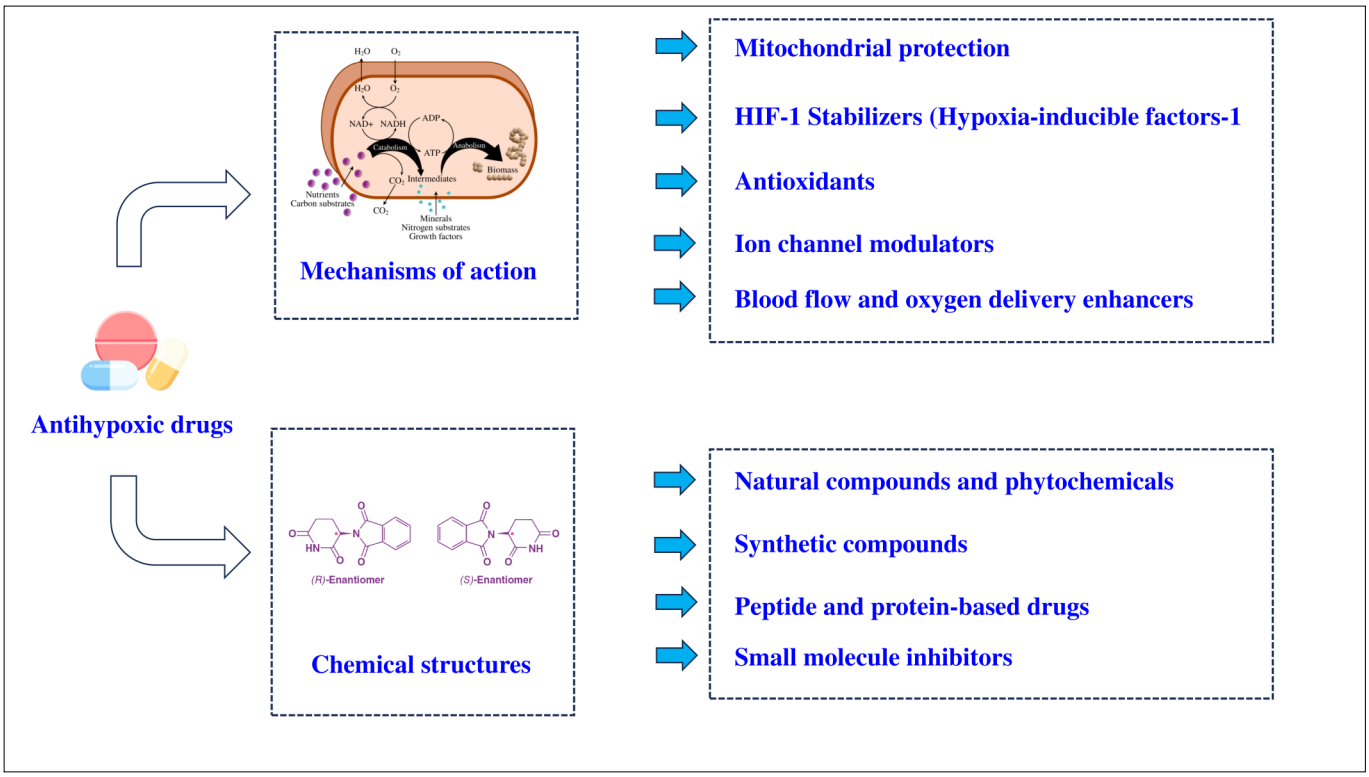

Fig. 1. Classification of antihypoxic drugs.

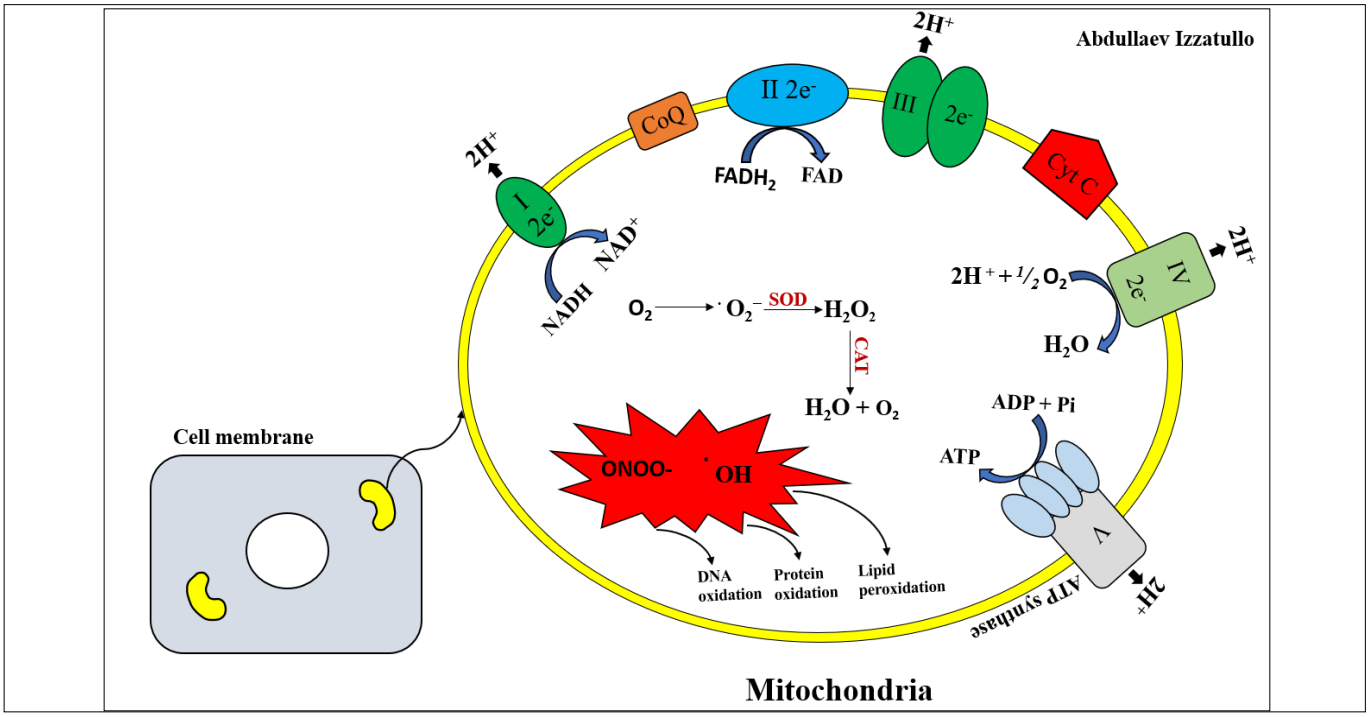

Fig. 2. Generation of ROS in mitochondrion. Mitochondrial electron transport chain (ETC) is composed of five multi-subunit enzyme complexes located in the inner mitochondrial membrane.

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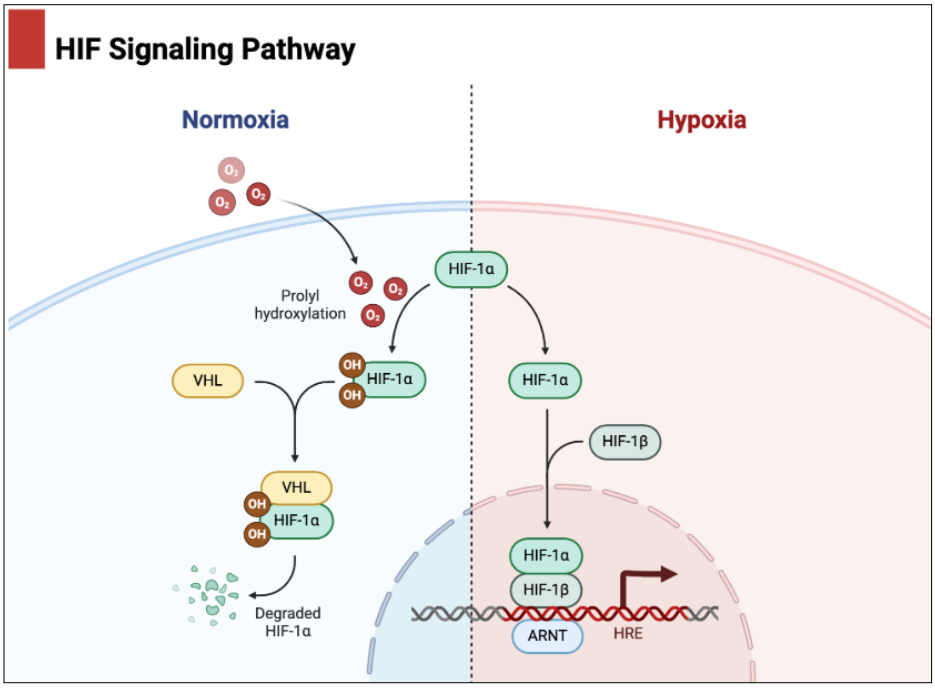

Fig. 3. Activation of HIF-1α and upregulation of gene expression.

Role in HIF-1 Signaling: Hypoxia-Inducible Factor-1 (HIF-1) is the master regulator of cellular responses to low oxygen levels. Under normoxic conditions, HIF-1α is rapidly degraded, but during hypoxia, it stabilizes and activates genes involved in oxygen homeostasis, angiogenesis, erythropoiesis and metabolic adaptation (Table 1). Antihypoxic drugs that target the HIF-1 pathway either stabilize HIF-1α or mimic its effects (15, 16).

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Metabolic adaptation: By activating HIF-1, these drugs also promote metabolic shifts that allow cells to survive in low-oxygen environments. HIF-1 induces glycolytic enzymes, facilitating a switch from oxidative phosphorylation to anaerobic glycolysis, ensuring that cells can produce energy even when oxygen is limited (17, 18).

Antioxidants: These drugs scavenge ROS generated during hypoxia, preventing oxidative damage to cells and tissues (Fig. 4). Antioxidants play a protective role by maintaining redox balance and reducing lipid peroxidation. Examples: vitamin E, ascorbic acid, N-acetylcysteine (NAC) (19, 20).

Ion channel modulators: Certain antihypoxic drugs target ion channels, particularly potassium and calcium channels, to stabilize the membrane potential and reduce cellular damage (21, 22). These drugs regulate the activity of channels like mitoK-ATP and calcium channels, which play a key role in hypoxic stress. Examples: Nicorandil (K-ATP channel opener), calcium channel blockers (23, 24).

Ion channels and calcium homeostasis: Ion channels, particularly those regulating potassium and calcium ions, play a vital role in cellular response to hypoxia. Dysregulation of ion channels during hypoxia leads to calcium overload, membrane depolarization and cell death. Antihypoxic drugs modulate these channels to prevent hypoxia-induced cellular damage.

Potassium channels: Drugs like nicorandil target ATP-sensitive potassium (K-ATP) channels in both the mitochondria and plasma membranes. Opening of K-ATP channels during hypoxia helps to stabilize membrane potential and reduce cellular excitotoxicity (25, 26).

Calcium channels: Calcium overload is a common consequence of hypoxia, leading to mitochondrial dysfunction and apoptosis. Calcium channel blockers like nifedipine reduce calcium influx into cells, maintaining calcium homeostasis and protecting against hypoxia-induced cell damage. By regulating intracellular calcium levels, these drugs prevent mitochondrial permeability transition and preserve cell viability (27, 28).

Metabolic modulators: These drugs shift the metabolic balance toward anaerobic glycolysis or enhance glucose utilization, allowing cells to produce energy more efficiently in low-oxygen environments. Examples: Dichloroacetate (DCA), trimetazidine (metabolic modulator) (29, 30) (Table 2).

Table 1. Biomarkers and molecular pathways activated in hypoxic conditions. This table can summarize key biomarkers, molecular pathways and their roles during hypoxia, along with the respective drugs targeting those pathways

Biomarker	Pathway	Role in hypoxia	Target drug
HIF-1α	HIF-1 pathway	Oxygen-sensing and adaptation	Roxadustat
ROS	Antioxidant system	Promotes oxidative stress	Vitamin E
VEGF	Angiogenesis pathway	Stimulates new blood vessel formation	Vadadustat

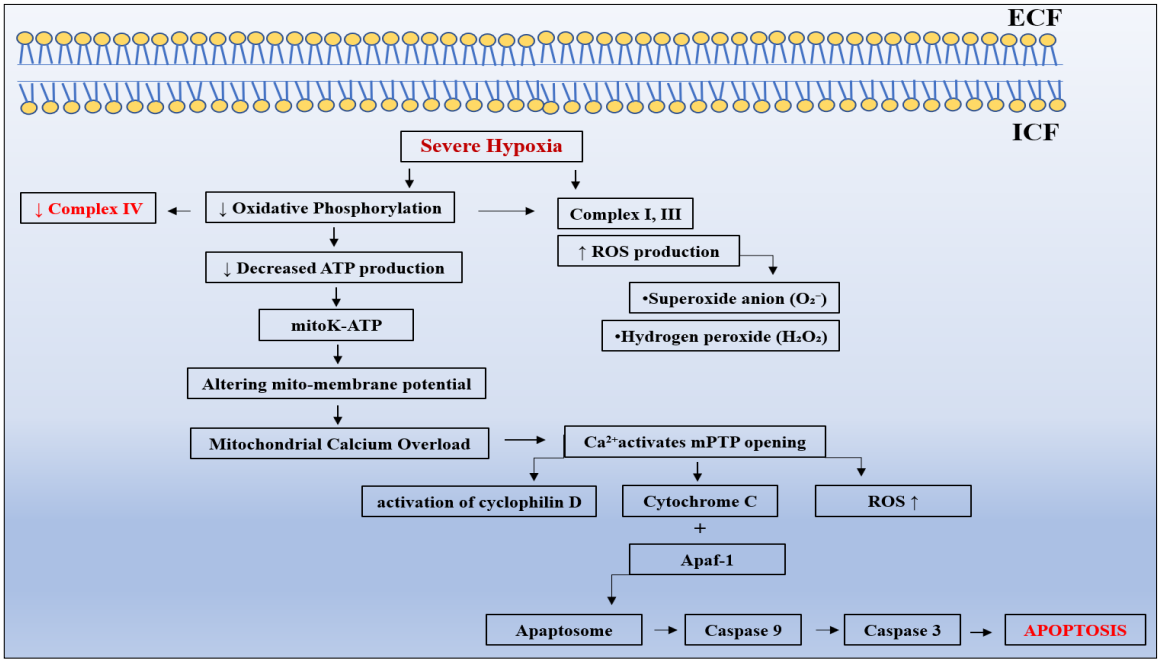

Fig. 4. Hypoxia-mediated induction of ROS and apoptosis.

Table 2. Adaptive pathways influenced by antihypoxic drugs

Adaptive pathway	Target drug	Effect on cellular adaptation	Mechanism
Mitochondrial efficiency	Nicorandil	Maintains mitochondrial membrane potential, preventing cell death	Modulates mitoK-ATP channels to preserve ATP production during oxygen shortage
HIF-1α stabilization	Roxadustat, Vadadustat	Promotes angiogenesis and metabolic reprogramming	Inhibits degradation of HIF-1α, activating adaptive genes like VEGF
Antioxidant defense	N-acetylcysteine, Vitamin E	Enhances ROS detoxification, reducing oxidative damage	Boosts glutathione levels and activates endogenous antioxidant systems
Metabolic reprogramming	Trimetazidine, DCA	Shifts metabolism from oxidative phosphorylation to glycolysis	Inhibits fatty acid oxidation and promotes glucose metabolism
Calcium homeostasis	Nifedipine, Nicorandil	Maintains intracellular calcium balance, preventing mitochondrial damage	Reduces calcium influx, stabilizes mitochondrial function under hypoxia
Oxygen delivery	Nitroglycerin, Pentoxifylline	Improves perfusion and oxygen transport to hypoxic tissues	Vasodilation and microcirculatory improvements ensure better oxygen supply

Antihypoxic drugs exert their therapeutic effects through various molecular pathways aimed at counteracting the detrimental effects of oxygen deprivation. These mechanisms target mitochondrial function, cellular signaling, redox balance, ion channel regulation, blood flow and metabolic pathways to protect tissues from hypoxic damage. Below are the key mechanisms through which these drugs function (31, 32).

Blood flow regulation

Effective oxygen delivery to tissues is essential during hypoxic conditions. Antihypoxic drugs that improve blood flow by increasing vasodilation play a critical role in enhancing oxygen delivery to hypoxic tissues, preventing ischemic damage (33, 34).

Vasodilators: Drugs such as nitroglycerin and sodium nitroprusside promote the production of nitric oxide (NO), a potent vasodilator that relaxes vascular smooth muscle (Table 3). This leads to increased blood flow and improved oxygen delivery to ischemic tissues, alleviating the effects of hypoxia (35, 36).

Pentoxifylline: This drug improves blood flow by reducing blood viscosity and enhancing the deformability of red blood cells, allowing for better perfusion in microvascular networks under hypoxic conditions (37, 38).

Impact on mitochondrial function

Mitochondria are crucial for cellular energy production, generating ATP through oxidative phosphorylation (39, 40). Under hypoxic conditions, mitochondrial function is severely compromised, leading to the production of ROS and subsequent oxidative damage. Antihypoxic drugs that target mitochondria focus on two main aspects: reducing oxidative stress and preserving ATP synthesis (41, 42).

Regulating oxidative stress: During hypoxia, the ETC becomes dysfunctional, resulting in excessive ROS production. Antioxidant-based drugs, such as Coenzyme Q10 and L-carnitine, protect mitochondrial membranes from lipid peroxidation and prevent oxidative damage to cellular components, preserving mitochondrial integrity and functionality (43).

Table 3. Comparative efficacy of antihypoxic drugs in different hypoxic conditions

Conditions	Drugs	Outcome	Effective doses
Ischemia	Nitroglycerin	Increases blood flow	Preserves mitochondrial potential
Stroke	Pentoxifylline	Improves microcirculation	Preserves mitochondrial potential
Hypoxia-reperfusion injury	Nicorandil	Preserves mitochondrial potential	10 mg

Redox balance and antioxidant effects: Hypoxia results in increased ROS production, which causes oxidative damage to proteins, lipids and DNA, exacerbating tissue injury. Antihypoxic drugs with antioxidant properties are designed to counteract ROS, thereby preventing oxidative stress and its associated cellular damage.

Scavenging ROS: Antioxidant compounds, such as vitamin E, ascorbic acid (vitamin C) and N-acetylcysteine (NAC), neutralize ROS by donating electrons, thereby reducing oxidative stress. These compounds also restore cellular redox balance by regenerating intracellular antioxidant systems like glutathione (Table 2).

Metabolic reprogramming

Under hypoxia, oxidative phosphorylation is inhibited due to the lack of oxygen as the final electron acceptor in the ETC. To adapt, cells switch to anaerobic glycolysis for ATP production. Antihypoxic drugs that modulate metabolic pathways promote this shift, ensuring continued energy production in oxygen-deprived cells.

Based on chemical structures

Natural compounds and phytochemicals: Many natural compounds derived from medicinal plants exhibit antihypoxic properties (Table 4). These compounds often act as antioxidants or mitochondrial protectors (44, 45). Examples: *Rhodiola heteradonta* (adaptogen), polyphenols (e.g., resveratrol) (Fig. 5).

Synthetic compounds: These are chemically synthesized drugs specifically designed to target hypoxia pathways. They often stabilize HIF-1, protect mitochondria, or act as antioxidants. Examples: Methylprednisolone, desidustat, synthetic HIF-1 stabilizers (46, 47).

Peptide and protein-based drugs: These drugs include erythropoietin and other proteins that act to improve oxygen-carrying capacity or promote adaptive responses to hypoxia. Examples: Erythropoietin (EPO), angiopoietin mimetics

Small molecule inhibitors: These are small molecule drugs that inhibit specific pathways or enzymes related to hypoxic damage, such as prolyl hydroxylase inhibitors that stabilize HIF- Examples: Molidustat, daprodustat.

This classification helps to systematically understand how antihypoxic drugs work and what their underlying chemical structures are, providing insights into their therapeutic potential for conditions like ischemia, stroke and chronic hypoxic diseases (48, 49).

Influence of chemical structures on the therapeutic efficacy of antihypoxic agents

The therapeutic efficacy of antihypoxic agents is intricately linked to their chemical structures, which determine their interaction with biological targets, bioavailability and stability. Understanding the structure-activity relationship (SAR) helps design more potent and selective compounds to counteract hypoxia-induced damage (50). Below are some key areas where chemical structures play a crucial role:

1. Lipid solubility and membrane penetration

Mechanism: Antihypoxic agents must penetrate cellular membranes, especially mitochondrial membranes, to exert protective effects (Fig. 6). Lipophilic (fat-soluble) compounds tend to have higher permeability through the lipid bilayers of cell membranes, enhancing their ability to reach intracellular targets like mitochondria (51, 52).

Example: The lipophilicity of Coenzyme Q10 and other quinone-based molecules enhances their ability to localize in the

Table 4. Antihypoxic drugs based on chemical structures

Compound phytochemical	Source	Chemical Structures	Mechanism of action	Adaptive antihypoxic properties
Rhodiola heteradonta (Adaptogen)	*Rhodiola heteradonta*	Phenolic glycosides	Enhances mitochondrial function, antioxidant activity	Protects against oxidative stress, improve cellular resilience to hypoxia
Ginsenosides	Ginseng (*Panax ginseng*)	Triterpene saponins	Modulates ion channels, antioxidant defense	Promote energy efficiency, enhances blood flow, protects mitochondria
Resveratrol	Grapes, red wine	Polyphenols	Activates SIRT1, enhances mitochondrial biogenesis	Reduces oxidative stress, promotes metabolic reprogramming during hypoxia
Curcumin	Turmeric (*Curcuma longa*)	Polyphenolic curcuminoid	Inhibits ROS production, enhances antioxidant enzymes	Protects against hypoxia-induced oxidative damage, supports cell survival
Quercetin	Various fruits & vegetables	Flavonoid	Inhibits pro-inflammatory cytokines, boosts antioxidant enzymes	Enhances HIF-1 stabilization, reduces oxidative damage during hypoxia
Epigallocatechin gallate (EGCG)	Green tea (*Camellia sinensis*)	Catechin	Reduces ROS generation, inhibits mitochondrial dysfunction	Prevents oxidative damage, supports mitochondrial stability in hypoxia
Salvianolic acid B	*Salvia miltiorrhiza*	Polyphenolic acid	Scavenges free radicals, inhibit lipid peroxidation	Protects mitochondria, promotes antioxidant capacity under hypoxia
Berberine	Berberis species	Isoquinoline alkaloid	Modulates glucose metabolism, improves mitochondrial efficiency	Promotes glycolysis, reduces oxidative damage, stabilizes energy production
Naringin	Citrus fruits	Flavanone glycoside	Enhances mitochondrial biogenesis, reduces oxidative stress	Protects against hypoxic injury, improves mitochondrial adaptability
Hesperidin	Citrus fruits	Flavanone glycoside	Antioxidant and anti-inflammatory properties	Reduces oxidative stress, stabilizes cellular membranes during hypoxia

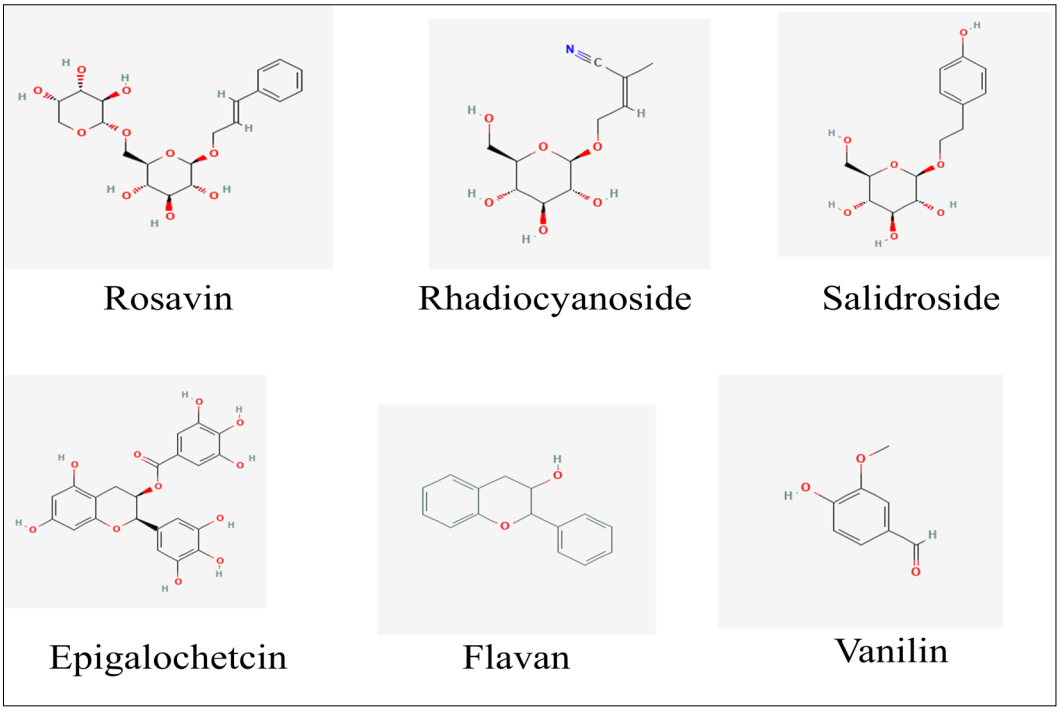

Fig. 5. Chemical structures of *Rhodiola heteradonta.*

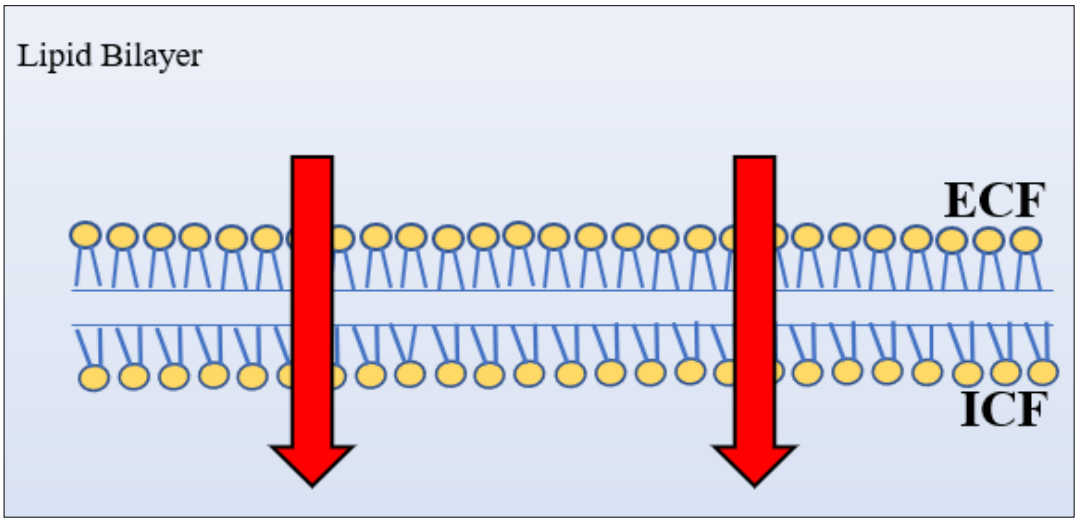

Fig. 6. Compound permeability across lipid bilayers.

mitochondrial membrane, where they can efficiently participate in electron transport and act as antioxidants (53, 54).

Improvement: Modifications that increase lipophilicity or include amphiphilic properties (both hydrophilic and hydrophobic) improve the capacity of these molecules to cross biological barriers.

2. Steric hindrance and receptor binding

Mechanism: The spatial arrangement (steric factors) of molecules influences how effectively they bind to their target receptors or enzymes. Drugs targeting HIF-1 stabilization or mitochondrial channels rely on a precise fit to their respective protein targets (55, 56).

Example: HIF-1 stabilizers like roxadustat feature specific steric configurations that allow them to inhibit prolyl hydroxylase enzymes, stabilizing the HIF-1α protein and preventing its degradation. This precise interaction is enabled by their cyclic structure, which provides a stable configuration for enzyme binding (57, 58).

Improvement: Modifying steric hindrance can either increase selectivity or reduce off-target effects, making the drug more potent and safer.

3. Functional groups and redox activity

Mechanism: Functional groups such as hydroxyl (-OH), carboxyl (-COOH) and thiol (-SH) groups influence the redox properties of a molecule, determining its ability to act as an antioxidant or modulate oxidative stress (58, 59).

Example: Antioxidants like NAC have a thiol group that can donate electrons to neutralize ROS. Similarly, polyphenols derived from plants contain hydroxyl groups that enable them to scavenge free radicals (60).

Improvement: Adding or modifying functional groups to improve the redox capacity can enhance the drug's ability to mitigate oxidative damage, a major consequence of hypoxia.

4. Conjugated systems and electron transport

Mechanism: Molecules with conjugated π-systems (alternating double and single bonds) are often involved in electron

transport, a critical process in mitochondrial function. Conjugation stabilizes free radicals or charges, making these molecules more effective in antioxidant or electron-transfer processes.

Example: The conjugated structure of Coenzyme Q10 allows it to participate efficiently in the mitochondrial ETC, facilitating ATP production even during hypoxia (61).

Improvement: Expanding the conjugation system or optimizing its resonance structure can increase the electron-transport efficiency of the drug.

5. Ring structures and stability

Mechanism: The presence of ring structures in chemical compounds influences both stability and receptor binding. Cyclic structures often confer rigidity to a molecule, allowing for more specific interactions with biological targets and improving resistance to metabolic breakdown (62).

Example: Nicorandil, a K-ATP channel opener, contains a nitrate ester linked to a ring structure, providing stability and controlled release of nitric oxide (NO) to induce vasodilation under hypoxic conditions.

Improvement: Incorporating heterocyclic rings (rings containing atoms like nitrogen or oxygen) can enhance binding affinity for ion channels or enzymes, improving the overall pharmacological profile.

6. Hydrogen bonding and solubility

Mechanism: Hydrogen bonding influences solubility, bioavailability and interaction with protein targets. Drugs that can form hydrogen bonds with cellular proteins or DNA exhibit better target specificity.

Example: Desidustat, a HIF-PHD inhibitor, forms critical hydrogen bonds with the prolyl hydroxylase enzyme, inhibiting it effectively to stabilize HIF-1α. These interactions are key to its hypoxia-mimicking effects (63).

Improvement: Modifying hydrogen-bond donors or acceptors on the molecule can enhance binding strength, solubility in aqueous environments, or intracellular distribution (64).

Implications for drug design and development

The ability to fine-tune chemical structures in antihypoxic agents is crucial for enhancing their effectiveness. Drug design strategies often focus on modifying specific regions of the molecule to:

Increase selectivity: Minimize off-target effects by designing drugs that specifically target mitochondrial pathways, HIF-1 signaling, or ion channels (65).

Enhance bioavailability: Improve solubility and membrane penetration through the addition of specific functional groups or by optimizing the molecular size and charge.

Improve pharmacokinetics: Prolong the half-life and stability of the drug in the body, ensuring sustained action under hypoxic conditions (66).

The mechanisms through which antihypoxic drugs exert their protective effects are diverse and target multiple pathways involved in oxygen homeostasis, mitochondrial function, redox balance, ion channel regulation, blood flow and metabolic adaptation. By understanding these mechanisms, we can better optimize therapeutic strategies for treating diseases associated with hypoxia, such as ischemia, stroke and heart failure and improve clinical outcomes for patients suffering from hypoxic conditions.

Molecular targets and mechanisms of action

Key molecular targets of antihypoxic drugs include mPTP, K-ATP channels, cardiovascular ion channels and the HIF-1α signaling pathway.

Mitochondrial function

mPTP regulation is critical in preserving mitochondrial integrity under hypoxia. Antihypoxic drugs stabilize mPTP, preventing mitochondrial depolarization, oxidative damage and cytochrome c release, which are precursors to apoptotic cell death. By modulating mitochondrial membrane potential and enhancing ATP production, these drugs ensure sustained cellular energy under oxygen limited conditions.

Ion channels

The role of K-ATP and other cardiovascular ion channels is equally vital. Drugs targeting K-ATP channels restore ionic balance, reduce calcium overload and improve vascular tone. These actions not only enhance cardiac contractility but also protect against reperfusion injury, a major consequence of ischemic events.

HIF-1α Stabilization

Stabilization of HIF-1α is another crucial mechanism, enabling cells to adapt by activating genes involved in angiogenesis, glycolysis and erythropoiesis. HIF-1α-stabilizing agents like roxadustat effectively inhibit prolyl hydroxylase enzymes, promoting oxygen-independent cellular survival pathways.

Structural optimization for enhanced efficacy

Structural modifications have significantly improved the pharmacological profiles of antihypoxic drugs. Enhancements in lipophilicity and amphiphilicity have increased their ability to cross biological barriers, while specific steric configurations have improved binding to protein targets. Functional groups with redox activity, such as hydroxyl and thiol groups, enhance antioxidant properties, mitigating oxidative damage associated with hypoxia. Furthermore, the incorporation of conjugated systems and ring structures has optimized electron transport efficiency and molecular stability, critical for maintaining mitochondrial function.

Classification and mechanistic diversity

Antihypoxic drugs can be classified based on their primary mechanisms of action, such as mitochondrial protectors, ion channel modulators, HIF-1α stabilizers and redox-active agents. This classification provides a framework for understanding their diverse therapeutic effects and for designing combination therapies to target multiple hypoxia-related pathways simultaneously.

Clinical implications and future directions

The therapeutic potential of antihypoxic drugs extends beyond acute hypoxic conditions to chronic diseases like heart failure and neurodegenerative disorders, where hypoxia-driven cellular dysfunction is a significant contributor. Advances in drug design focusing on selectivity, bioavailability and reduced off-target effects have paved the way for safer and more effective

therapies.

Future research should aim to develop novel agents targeting unexplored molecular pathways, such as non-canonical HIF signaling and to refine drug delivery systems to ensure site-specific action. Moreover, understanding the interplay between these drugs and other cellular mechanisms, such as inflammation and immune responses, could further expand their therapeutic applications.

Results and Discussion

Antihypoxic drugs have emerged as essential therapeutic agents in addressing the cellular and systemic challenges posed by oxygen deprivation in pathological conditions such as ischemia, stroke and heart failure. Their effectiveness lies in targeting molecular mechanisms that govern oxygen sensing, mitochondrial function and cellular adaptation to hypoxia. This discussion explores the implications of these drugs on specific molecular targets and highlights the advancements in drug design strategies to enhance their therapeutic efficacy.

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Authors' contributions

Concept, design, analysis, interpretation, data collection, writing the article, statistical analysis were done by IZOA. Critical revision of the article, final approval of the article and overall responsibility were performed by UGG and FAS. Data collection, statistical analysis, analysis and interpretation were done by SZO and AAOA. SNG collects the data and performs the critical revision of the article. TFA obtained funding, overall responsibility, final approval of the article. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work we have used quillbot.com in order to check plagiarism.

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