REVIEW ARTICLE OPEN ACCESS

Targeting Hypoxia-Induced Oxidative Stress via Natural Antioxidant Modulation: From Cellular Signaling to Therapeutic Perspectives

Dwi Widyawati[1], Ghea Farmaning Thias Putri[2]*, Rifdah Hanifah[3], Firda Asmaul Husna[2], Nabila Aulia Tsaqifah[4], Ainina Al Shadrina[5]

*Correspondence:
ghea.farmaning@untirta.ac.id

[1]*Department of Physiology, Faculty of Medicine and Health Science, Sultan Ageng Tirtayasa University, Banten 42118, Indonesia.*
[2]*Department of Medical Biology, Faculty of Medicine and Health Science, Sultan Ageng Tirtayasa University, Banten 42118, Indonesia*
[3]*Department of Microbiology, Faculty of Medicine and Health Science, Sultan Ageng Tirtayasa University, Banten 42118, Indonesia.*
[4]*Department of Public Health, Faculty of Medicine and Health Science, Sultan Ageng Tirtayasa University, Banten 42118, Indonesia.*
[5]*Department of Pharmacy, Faculty of Medicine and Health Science, Sultan Ageng Tirtayasa University, Banten 42118, Indonesia*

Submission October 17, 2025
Accepted December 06, 2025
Available online on December 22, 2025

ABSTRACT

Hypoxia is a fundamental physiological and pathological condition that disrupts cellular homeostasis through the excessive generation of reactive oxygen species (ROS), leading to oxidative stress, inflammation, and organ dysfunction. The imbalance between ROS production and antioxidant defense mechanisms is a key contributor to cell injury and disease progression. This review aims to elucidate the molecular interactions among major redox-sensitive signaling pathways, hypoxia-inducible factor 1 (HIF-1), nuclear factor kappa B (NF-κB), and nuclear factor erythroid 2-related factor 2 (Nrf2) in hypoxia-induced oxidative stress, and to highlight the therapeutic potential of natural antioxidants in modulating these pathways. Relevant literature published over the past five years (2020-2025) was systematically reviewed using databases including PubMed, Scopus, and ScienceDirect. The selected studies focused on molecular redox signaling, hypoxia-induced oxidative mechanisms, and the modulatory roles of natural phytochemicals such as *Ficus carica* bioactive compounds. Recent findings reveal that natural antioxidants regulate redox signaling by activating Nrf2-dependent antioxidant responses, suppressing NF-κB-driven inflammation, and stabilizing HIF-1α under hypoxic conditions. Phytochemicals, particularly flavonoids and polyphenols, exhibit strong potential to restore oxidative balance, protect cellular integrity, and reduce hypoxia-induced damage. Modulating hypoxia-induced oxidative stress through natural antioxidant pathways offers a promising therapeutic strategy. A deeper understanding of the molecular crosstalk between redox signaling and phytochemical activity may provide new insights for developing preventive and therapeutic interventions against hypoxia-related disorders.

Keywords: Hypoxia, Oxidative stress, Nrf2.

INTRODUCTION

Oxygen is a vital substrate for cellular respiration and energy generation, and its homeostasis is tightly regulated under physiological conditions. Reduced oxygen availability known as hypoxia induces metabolic and redox imbalances that compromise normal cellular function and promote pathophysiological processes. Hypoxia is implicated in a wide range of diseases, including ischemic injury, non-alcoholic fatty liver disease (NAFLD), cancer, and chronic inflammatory disorders [1]. Under hypoxic stress, excessive generation of reactive oxygen species (ROS) overwhelms endogenous antioxidant systems, resulting in oxidative damage to lipids, proteins, and nucleic acids, ultimately leading to apoptosis and tissue dysfunction [2,3].

Cells respond to hypoxia-induced oxidative stress via activation of several redox-sensitive signaling pathways. Among these, hypoxia-inducible factor-1 (HIF-1), nuclear factor kappa B (NF-κB), and nuclear factor erythroid 2-related factor 2 (Nrf2) play crucial and interconnected roles [4,5]. HIF-1 mediates adaptive responses by regulating genes involved in angiogenesis and energy metabolism, NF-κB orchestrates inflammatory and immune processes, while Nrf2 acts as the master regulator of endogenous antioxidant defense by inducing enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)[6,7]. Dysregulation or imbalance among these pathways under hypoxia can exacerbate oxidative injury, contributing to disease progression in multiple organ systems[8].

Conventional antioxidant therapies often show limited efficacy due to low bioavailability, poor pharmacokinetics, and insufficient targeting of redox signaling[9]. Therefore, there has been growing interest in natural phytochemicals as modulators of oxidative stress and hypoxia-related pathways. Bioactive plant compounds such as flavonoids, polyphenols, and anthocyanins are known to modulate cellular signaling and enhance endogenous antioxidant capacity[10]. For instance, our recent study demonstrated that *Ficus carica* dietary supplementation ameliorated cognitive impairment and oxidative stress in hypoxia-induced NAFLD, likely via modulation of antioxidant signaling[11]. Similarly, *Ficus carica* puree was shown to elevate antioxidant enzyme activities and reduce lipid peroxidation in lung tissues subjected to intermittent hypoxia[12]. In kidney tissue, *Ficus carica* intervention in rats subjected to chronic intermittent hypoxia significantly reduced malondialdehyde (MDA) levels and increased superoxide dismutase (SOD) activity, demonstrating the protective antioxidative effect of *Ficus carica* under hypoxic stress[1]. Other studies also report that phytochemicals such as 6-hydroxyginseng protect neural PC12 cells against hypoxia-induced oxidative injury via activation of Nrf2/HO-1 signaling[3], while modulation of HIF-1α and NF-κB cross-talk has been observed in ischemic and hypobaric hypoxia models[4,5].

Even while there is growing evidence that natural antioxidants reduce oxidative stress caused by hypoxia, most of the material now in publication focuses on individual signaling pathways, specifically HIF-1, NF-κB, or Nrf2. There is still a lack of a mechanistic synthesis that incorporates the dynamic crosstalk between these redox-sensitive pathways in hypoxic environments. Moreover, while *Ficus carica* has consistently demonstrated cytoprotective and antioxidative properties in hypoxia-related models, its role as a multi-target modulator that coordinates various interrelated signaling pathways has not been comprehensively investigated. To close this gap, the current review incorporates new molecular and experimental data (2020–2025) to clarify how *Ficus carica* and similar phytochemicals coordinate the regulation of HIF-1, NF-κB, and Nrf2 signaling to orchestrate redox homeostasis.

MATERIALS AND METHODS

Literature Search Strategy

A comprehensive literature search was performed to identify relevant studies discussing hypoxia-induced oxidative stress, redox-sensitive signaling pathways, and the modulatory effects of natural antioxidants, particularly *Ficus carica* and related phytochemicals. The search covered publications from January 2020 to February 2025, using the electronic databases PubMed, Scopus, ScienceDirect, and Google Scholar. The search strategy employed combinations of the following keywords: “hypoxia”, “oxidative stress”, “HIF-1 signaling”, “Nrf2 pathway”, “NF-κB”, “redox regulation”, “natural antioxidants”, “phytochemicals”, “*Ficus carica*”, and “intermittent hypoxia”.

Inclusion criteria consisted of:

1. Original research and review articles published between 2020-2025.
2. Studies written in English and accessible in full text.
3. Research focusing on cellular, molecular, or biochemical mechanisms of hypoxia and redox modulation.
4. Experimental or review studies evaluating the antioxidant or signaling effects of *Ficus carica* or comparable phytochemicals.

Exclusion criteria included:

1. Articles published before 2020, and non-peer-reviewed materials, editorials, or conference abstracts lacking experimental data.

Data were extracted on study design, model type (in vitro, in vivo, or clinical), major findings on oxidative biomarkers (e.g., SOD, CAT, GPx, MDA), and effects on signaling pathways (HIF-1, NF-κB, Nrf2). Comparative evaluation was performed to integrate emerging evidence linking natural antioxidant activity with hypoxia-related cellular adaptation and tissue protection.

The search identified several key studies highlighting the antioxidative and cytoprotective roles of *Ficus carica* under hypoxic stress[11,12], as well as contemporary evidence showing that other phytochemicals such as 6-hydroxygingerol and resveratrol can regulate Nrf2/HO-1 and HIF-1 pathways to attenuate oxidative injury[3,4]. All selected references were cross-checked for relevance and scientific validity according to SCCR editorial standards, ensuring that only peer-reviewed literature from reputable journals and proceedings (including Kobe Journal of Medical Sciences, Journal of Medical Sciences, and INSPIGHRES Proceedings) was included. The preliminary database search produced 214 records. Following the elimination of duplicates and a review of titles and abstracts, 86 articles were evaluated for full-text eligibility. Forty studies fulfilled the established inclusion criteria and were incorporated into the final qualitative synthesis.

RESULTS

HIF-1 Signaling Under Hypoxia

Hypoxia-inducible factor-1 (HIF-1) functions as the central oxygen-sensing transcription factor mediating cellular adaptation to reduced oxygen availability. Under hypoxic conditions, suppression of prolyl hydroxylase domain (PHD) enzyme activity results in stabilization of HIF-1α, its heterodimerization with HIF-1β, and transcriptional activation of genes involved in angiogenesis, glucose metabolism, and erythropoiesis[3,12,13]. Experimental evidence indicates that prolonged HIF-1 activation is closely connected with mitochondrial dysfunction and increased reactive oxygen species (ROS) production, hence worsening oxidative stress in hypoxia-exposed tissues[14].

Multiple cellular and animal investigations reveal that mitochondrial ROS further strengthen HIF-1α stability by blocking PHD activity, producing a feed-forward loop that enhances hypoxia-induced oxidative injury[15]. In hepatic models subjected to intermittent hypoxia, dysregulated HIF-1 signaling has been linked to altered mitochondrial biogenesis and increased lipid peroxidation[9]. Phytochemical therapies have demonstrated efficacy in mitigating this maladaptive reaction. Supplementation with *Ficus carica* extracts specifically decreased HIF-1α protein expression and oxidative stress indicators in liver and kidney tissues subjected to hypoxia, indicating that regulation of ROS-dependent HIF-1 signaling may mitigate hypoxia-induced tissue damage[6,7,9]. Similar regulatory impacts on HIF-1α stabilization have been documented for polyphenolic substances, including resveratrol and quercetin, thereby reinforcing HIF-1 as a redox-sensitive therapeutic

target[11,12]. These findings from phytochemical interventions underscore HIF-1 as a viable biochemical target for mitigating oxidative stress in hypoxia-related disorders, with potential for affordable, plant-based therapies in resource-limited settings.

NF-κB Pathway and Inflammatory Balance

Hypoxic stress triggers a coordinated redox-inflammation response, marked by the activation of nuclear factor kappa B (NF-κB) signaling and the compensatory induction of antioxidant pathways regulated by nuclear factor erythroid 2-related factor 2 (Nrf2). The accumulation of reactive oxygen species (ROS) during hypoxia facilitates the activation of NF-κB, resulting in enhanced transcription of pro-inflammatory cytokines and enzymes that exacerbate oxidative injury[16,17]. Simultaneously, oxidative modification of Keap1 impairs the Keap1-Nrf2 complex, promoting Nrf2 nuclear translocation and the activation of antioxidant defense genes[18,19].

Nrf2 activation counteracts NF-κB-mediated inflammation by competing for common transcriptional co-activators and inhibiting the expression of pro-inflammatory cytokines, while also restoring mitochondrial function via PGC-1α-related pathways[20,21]. Flavonoid-rich extracts from *Ficus carica* provide evidence for the direct activation of Nrf2 signaling through the modification of Keap1 cysteine, leading to increased expression of antioxidant enzymes, including heme oxygenase-1 (HO-1), in hypoxic models[3,7,23]. Moreover, these compounds exert dual regulation by concurrently activating the Nrf2 antioxidant pathway (via Keap1 dissociation), restoring redox homeostasis, and mitigating inflammation[24,25]. In Sprague Dawley rats exposed to hypoxia, supplementation with oral *Ficus carica* puree significantly increased nuclear Nrf2 levels, enhanced antioxidant enzyme activity, and decreased malondialdehyde (MDA) accumulation, demonstrating effective reduction of oxidative injury[6.26,27]. Similar dual modulation of Nrf2 activation and NF-κB inhibition has been documented for other phytochemicals, such as resveratrol and 6-hydroxygenistein, in various cellular hypoxia models. The findings collectively indicate that the NF-κB–Nrf2 axis serves as a crucial regulatory interface for managing inflammatory and antioxidant responses during hypoxic stress [3,31,32].

Integrated Redox Signaling and Therapeutic Perspectives

Evidence suggests that cellular responses to hypoxia are regulated by a cohesive redox signaling network that includes HIF-1, NF-κB, and Nrf2. HIF-1 and NF-κB primarily facilitate adaptive metabolic and inflammatory responses; however, prolonged activation of these pathways leads to increased ROS production, persistent inflammation, and tissue damage[7,9,30,38]. Nrf2 serves as a primary counter-regulatory pathway that reestablishes redox homeostasis and mitigates inflammatory signaling via coordinated antioxidant induction[25]. Phytochemicals from *Ficus carica* demonstrate multitarget activity by concurrently enhancing Nrf2-mediated antioxidant defenses, inhibiting NF-κB-driven inflammation, and modulating ROS-dependent HIF-1α stabilization[6,7,35]. This coordinated regulation facilitates the restoration of redox balance in various organs affected by hypoxic stress, such as liver, lung, and kidney tissues[8]. The mechanistic actions of major *Ficus carica* bioactive compounds on hypoxia-induced redox signaling pathways are summarized in Table 1, highlighting their coordinated regulation of Nrf2 activation, NF-κB inhibition, and modulation of HIF-1α stabilization.

Table 1. Mechanistic effects of *Ficus carica* bioactive compounds on hypoxia-induced redox signaling pathways

No	Bioactive compound	Primary target pathway	Molecular mechanism	Functional outcome under hypoxia	Experimental model	Key references
1	Quercetin	NF-κB	Inhibition of IKKβ phosphorylation and prevention of IκBα degradation, leading to reduced nuclear translocation of p65	Decreased pro-inflammatory cytokines (TNF-α, IL-6), attenuation of hypoxia-induced inflammation	Rat intermittent hypoxia; hypoxic hepatic tissue	**Fitri et al., 2024; Guo et al., 2024; Gao et al., 2022**
2	Luteolin	Nrf2	Electrophilic modification of Keap1 cysteine residues (Cys151, Cys273), facilitating Nrf2 nuclear translocation and ARE activation	Increased antioxidant enzymes (HO-1, SOD, CAT), enhanced cellular redox defense	In vivo hypoxia models	**Huang et al., 2023; Sengul-Binat, 2025; Widyawati et al., 2025**
3	Anthocyanins	HIF-1	Reduction of mitochondrial ROS production, limiting PHD inhibition and preventing excessive HIF-1α stabilization	Reduced lipid peroxidation (↓ MDA), improved mitochondrial integrity	Hypoxic liver and lung models	**Fitri et al., 2024; Anggraini et al., 2025; Bae et al., 2024**
4	Polyphenols (mixed extract)	Integrated crosstalk (Nrf2–NF-κB–HIF-1)	Concurrent activation of Nrf2-ARE signaling, suppression of NF-κB activation, and modulation of ROS-dependent HIF-1α stabilization	Restoration of redox homeostasis, reduced inflammation, improved tissue resilience	Multi-organ hypoxia models (liver, lung, kidney)	**Widyawati et al., 2025; Kanner, 2020; Fazel et al., 2024**

DISCUSSION

Modulation of HIF-1 Signaling in Hypoxic Oxidative Stress

In alignment with the findings, HIF-1 signaling functions as a dual regulator under hypoxic conditions, facilitating crucial adaptive responses while also leading to oxidative injury upon chronic activation[12,13]. Sustained HIF-1α stabilization, rather than acting in isolation, enhances mitochondrial reactive oxygen species production, which exacerbates redox imbalance and contributes to tissue damage [9,15]. In this context, phytochemicals like *Ficus carica* seem to regulate HIF-1 signaling by reducing excessive ROS-dependent stabilization while maintaining adaptive hypoxic responses[7–9,12,11]. This specific mechanism of action differentiates natural antioxidants from traditional HIF-1 inhibitors and underscores their potential use in disorders related to chronic hypoxia [8,35].

NF-κB Pathway as a Mediator of Hypoxia-Induced Inflammation

In hypoxic environments, NF-κB signaling serves as a key inflammatory amplifier that connects redox imbalance to tissue damage. Transient activation of NF-κB plays a role in adaptive immune and stress responses; however, prolonged activation in chronic hypoxia leads to excessive inflammatory signaling, which exacerbates oxidative damage and disrupts cellular homeostasis[12,17]. This dual role positions NF-κB not only as an inflammatory switch but also as a context-dependent regulator, with its pathological impact primarily arising under prolonged hypoxic stress [18,19].

This review emphasizes that NF-κB activity in hypoxic conditions is closely regulated by antioxidant signaling, especially through reciprocal interactions with the Nrf2 pathway. NF-κB and Nrf2 do not operate independently; instead, they establish a dynamic regulatory axis where antioxidant activation inhibits inflammatory transcriptional programs and restores redox balance [20–22]. This interaction indicates that effective therapeutic strategies should focus on rebalancing NF-κB signaling instead of completely inhibiting it [3,7,23].

Phytochemicals like *Ficus carica* exhibit a regulatory advantage by simultaneously reducing NF-κB-driven inflammation and boosting antioxidant defenses [24,25]. This dual modulation differentiates phytochemical-based interventions from traditional anti-inflammatory methods that focus solely on NF-κB, potentially compromising vital adaptive responses. The capacity of *Ficus carica* to modulate inflammatory signaling within a redox-regulated framework highlights its significance in addressing hypoxia-related inflammatory disorders, especially in the contexts of chronic and metabolic diseases.

Nrf2/Keap1 Axis and Restoration of Cellular Redox Homeostasis

Nrf2 serves as a key integrative regulator in hypoxic environments, coordinating antioxidant defense, maintaining mitochondrial integrity, and restraining inflammation[26,27]. Nrf2 functions not only as an inducer of antioxidant enzymes but also as a systems-level modulator that counteracts redox and inflammatory pressures arising from prolonged hypoxic stress[34]. The expanded regulatory function is particularly apparent in chronic hypoxia, where insufficient activation of Nrf2 correlates with ongoing oxidative damage and metabolic impairment [20,28,29]. This review highlights that effective redox adaptation in hypoxic conditions relies on the functional interaction between Nrf2 and other stress-responsive pathways, notably NF-κB and HIF-1 [8,30]. Nrf2 plays a role in restoring cellular equilibrium by constraining pro-inflammatory transcriptional programs and indirectly limiting excessive hypoxia-driven signaling, rather than merely neutralizing reactive oxygen species [3,31]. This integrative positioning differentiates Nrf2 from downstream antioxidant effectors and highlights its significance as a therapeutic target. Phytochemical interventions, particularly those from *Ficus carica*, seem to utilize this regulatory ability by facilitating prolonged but regulated Nrf2 activation [33–35].

The intricate nature of *Ficus carica* phytochemicals may enhance Nrf2-mediated responses, promoting sustained redox stability while avoiding maladaptive suppression of hypoxia-responsive signaling. These properties are especially beneficial in multifactorial conditions linked to chronic hypoxia, where isolated antioxidant supplementation has demonstrated limited effectiveness.

Integrated Crosstalk between HIF-1, NF-κB, and Nrf2

This review emphasizes the coordinated interactions among HIF-1, NF-κB, and Nrf2, presenting them as a cohesive redox-regulatory network that regulates cellular adaptation to hypoxia. These pathways do not operate as isolated signaling modules; instead, they interact dynamically to ascertain whether hypoxic stress triggers adaptive responses or leads to oxidative injury and inflammation [36]. This integrative perspective emphasizes that therapeutic modulation of hypoxia-induced oxidative stress should focus on rebalancing pathway interactions rather than selectively inhibiting individual signaling nodes [37]. *Ficus carica* functions as a modulator that fine-tunes redox signaling networks by regulating antioxidant, inflammatory, and hypoxia-responsive pathways concurrently[25]. This systems-level modulation offers a framework that differentiates phytochemical interventions from traditional monotherapy.

Therapeutic Perspectives and Future Directions

This review synthesizes findings on HIF-1, NF-κB, and Nrf2 signaling, emphasizing the therapeutic potential of natural antioxidants, especially *Ficus carica*, in alleviating hypoxia-induced oxidative stress [20,37,40]. Functional food research further supports the preventive role of antioxidant-rich diets, suggesting that incorporating *Ficus carica* could offer a multifaceted approach to mitigating inflammation and metabolic imbalance in conditions like ischemia and metabolic syndrome[6], with particular relevance in tropical regions where such disorders are prevalent.

The varied phytochemical composition of *Ficus carica* facilitates the concurrent modulation of antioxidant defenses, inflammatory signaling, and hypoxia-responsive pathways, establishing it as a multitarget intervention for complex hypoxia-related disorders[25,26]. This coordinated mode of action may provide benefits compared to single-target antioxidant strategies, which frequently do not account for the interconnected aspects of redox dysregulation in hypoxic conditions. Despite promising preclinical findings, numerous translational challenges persist. The variability in phytochemical composition, limited bioavailability, and reliance on in vitro and animal models constrain the direct clinical applicability of existing findings. Variations in cultivation conditions and processing techniques can significantly affect the consistency of bioactive profiles in *Ficus carica*, highlighting the necessity for standardized formulations and stringent quality control measures [25,36].

Future research should focus on standardized formulations of *Ficus carica*, validation in clinically relevant hypoxia models (e.g., metabolic-associated fatty liver disease and ischemia–reperfusion injury), and the development of advanced delivery systems like nano-encapsulation to improve bioavailability and tissue targeting. The integration of molecular approaches, such as pathway-specific biomarkers and mechanistic modeling, could increase our knowledge about how phytochemicals derived from *Ficus carica* influence redox signaling networks in human pathophysiology.

CONCLUSION

Hypoxia-induced oxidative stress is governed by a closely linked signaling network that includes HIF-1, NF-κB, and Nrf2, rather than by the activation of separate pathways. The interplay among these redox-sensitive regulators dictates whether hypoxic stress triggers adaptive cellular responses or leads to chronic oxidative injury and inflammation. This review synthesizes evidence from the past five years, demonstrating that natural antioxidants, particularly those derived from *Ficus carica*, exert multitarget regulatory effects. These effects include enhancing Nrf2-mediated antioxidant defenses, restraining NF-κB-driven inflammation, and modulating ROS-dependent HIF-1 signaling. This systems-level perspective highlights the efficacy of phytochemical-based interventions in restoring redox homeostasis under hypoxic conditions compared to single-target strategies. These insights establish a conceptual basis for enhancing antioxidant-based strategies for hypoxia-related disorders and endorse further exploration of integrative redox modulation in translational research.

Competing Interests

The authors declare that they have no financial or non-financial conflicts of interest that could have influenced the content or outcomes of this article. They are solely responsible for the accuracy, integrity, and presentation of the data and interpretations provided, and no funding or external affiliations affected the research.

Authors' contributions

All authors contributed equally to the conceptualization, literature review, data acquisition and analysis, manuscript drafting, and critical revisions. All authors have reviewed, approved the final manuscript, and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

REFERENCES

1. Arias CF, Acosta FJ, Bertocchini F, Fernández-Arias C. Redefining the role of hypoxia-inducible factors (HIFs) in oxygen homeostasis. *Commun Biol*. 2025;8(1):446. doi:10.1038/s42003-025-07896-1
2. Guo Z, Tian Y, Liu N, et al. Mitochondrial Stress as a Central Player in the Pathogenesis of Hypoxia-Related Myocardial Dysfunction: New Insights. *Int J Med Sci*. 2024;21(13):2502-2509. doi:10.7150/ijms.99359
3. Xiao Y, Liu X, Xie K, et al. Mitochondrial dysfunction induced by HIF-1α under hypoxia contributes to the development of gastric mucosal lesions. *Clin Transl Med*. 2024;14(4). doi:10.1002/ctm2.1653
4. Woźniak Ł, Mierzejewska ŻA, Borys J, Ratajczak-Wrona W, Antonowicz B. Oxidative Stress and Biomarkers in Craniofacial Fractures Healing: From Lipid Peroxidation to Antioxidant Therapies. *Antioxidants*. 2025;14(9):1070. doi:10.3390/antiox14091070
5. Ulasov A V., Rosenkranz AA, Georgiev GP, Sobolev AS. Nrf2/Keap1/ARE signaling: Towards specific regulation. *Life Sci*. 2022;291:120111. doi:10.1016/j.lfs.2021.120111
6. Widyawati D, Meliala A, Siswanto, Narwidina P, Fitri AT. Dietary *Ficus carica* Inhibits Cognitive Impairment in Hypoxia-induced Non-alcoholic Fatty Liver Disease. *Kobe J Med Sci*. 2025;71(1):19-30.
7. Fitri AT, Meliala A, Widyawati D, Narwidina P, Siswanto S, Sumarno YT. *Ficus carica* Puree Exerts a Higher Antioxidative Profile in Hypoxic Lungs after Intermittently Inducing Hypoxia in Sprague–Dawley Rats. *J Med Sci*. 2024;44(6):262-268. doi:10.4103/jmedsci.jmedsci_39_24
8. Anggraini D, Meliala A, Siswanto, et al. Role of *Ficus carica* in Alleviating Chronic Hypoxia Impact in Rat's Lungs. *Indones J Hum Nutr*. 2025;11(2):142-152. doi:10.21776/ub.ijhn.2024.011.02.3
9. Kanner J. Polyphenols by Generating H2O2, Affect Cell Redox Signaling, Inhibit PTPs and Activate Nrf2 Axis for Adaptation and Cell Surviving: In Vitro, In Vivo and Human Health. *Antioxidants*. 2020;9(9):797. doi:10.3390/antiox9090797
10. Gao W, Guo L, Yang Y, et al. Dissecting the Crosstalk Between Nrf2 and NF-κB Response Pathways in Drug-Induced Toxicity. *Front Cell Dev Biol*. 2022;9. doi:10.3389/fcell.2021.809952
11. Guo Q, Jin Y, Chen X, et al. NF-κB in biology and targeted therapy: new insights and translational implications. *Signal Transduct Target Ther*. 2024;9(1):53. doi:10.1038/s41392-024-01757-9
12. Akinsulie OC, Shahzad S, Ogunleye SC, et al. Crosstalk between hypoxic cellular micro-environment and the immune system: a potential therapeutic target for infectious diseases. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1224102

13. Bae T, Hallis SP, Kwak MK. Hypoxia, oxidative stress, and the interplay of HIFs and NRF2 signaling in cancer. *Exp Mol Med*. 2024;56(3):501-514. doi:10.1038/s12276-024-01180-8

14. Cyran AM, Zhitkovich A. HIF1, HSF1, and NRF2: Oxidant-Responsive Trio Raising Cellular Defenses and Engaging Immune System. *Chem Res Toxicol*. 2022;35(10):1690-1700. doi:10.1021/acs.chemrestox.2c00131

15. Gaucher J, Vial G, Montellier E, et al. Intermittent Hypoxia Rewires the Liver Transcriptome and Fires up Fatty Acids Usage for Mitochondrial Respiration. *Front Med*. 2022;9. doi:10.3389/fmed.2022.829979

16. Wang R, Lv Y, Ni Z, et al. Intermittent hypoxia exacerbates metabolic dysfunction-associated fatty liver disease by aggravating hepatic copper deficiency-induced ferroptosis. *FASEB J*. 2024;38(13). doi:10.1096/fj.202400840R

17. Hu L, Hu J, Huang Y, et al. Hypoxia-mediated activation of hypoxia-inducible factor-1α in head and neck squamous cell carcinoma: A review. *Medicine (Baltimore)*. 2023;102(1):e32533. doi:10.1097/MD.0000000000032533

18. Saha S, Saso L. Pharmacological Modulation of Oxidative Stress. *Int J Mol Sci*. 2023;24(19):14455. doi:10.3390/ijms241914455

19. Zhang P, Zhang J, Ma C, Ma H, Jing L. 6-hydroxygenistein attenuates hypoxia-induced injury via activating Nrf2/HO-1 signaling pathway in PC12 cells. *Sci Rep*. 2025;15(1):875. doi:10.1038/s41598-025-85286-7

20. Huang W, Zhong Y, Gao B, Zheng B, Liu Y. Nrf2-mediated therapeutic effects of dietary flavones in different diseases. *Front Pharmacol*. 2023;14. doi:10.3389/fphar.2023.1240433

21. Bellanti F, Coda ARD, Trecca MI, Lo Buglio A, Serviddio G, Vendemiale G. Redox Imbalance in Inflammation: The Interplay of Oxidative and Reductive Stress. *Antioxidants*. 2025;14(6):656. doi:10.3390/antiox14060656

22. Romero-Durán MA, Silva-García O, Perez-Aguilar JM, Baizabal-Aguirre VM. Mechanisms of Keap1/Nrf2 modulation in bacterial infections: implications in persistence and clearance. *Front Immunol*. 2024;15. doi:10.3389/fimmu.2024.1508787

23. Hoang DM, Pham PT, Bach TQ, et al. Stem cell-based therapy for human diseases. *Signal Transduct Target Ther*. 2022;7(1). doi:10.1038/s41392-022-01134-4

24. Ravi, Singh J. Redox imbalance and hypoxia-inducible factors: a multifaceted crosstalk. *FEBS J*. 2025;292(15):3833-3848. doi:10.1111/febs.70013

25. Fazel MF, Abu IF, Mohamad MHN, et al. Physicochemistry, Nutritional, and Therapeutic Potential of *Ficus carica* – A Promising Nutraceutical. *Drug Des Devel Ther*. 2024;Volume 18:1947-1968. doi:10.2147/DDDT.S436446

26. Sengul-Binat H. Fig (*Ficus carica* L.) and its bioactive compounds. *J Agroaliment Process Technol*. 2025;2025 (31)(1):65-68. doi:10.59463/JAPT2025.1.7

27. Wardaya W, Sukmawati D, Ibrahim N, et al. Intermittent Exposure to Hypobaric Hypoxia Increases VEGF, HIF-1α, and Nrf-2 Expressions in Brain Tissue. *Indones Biomed J*. 2025;17(2):197-206. doi:10.18585/inabj.v17i2.3519

28. Ning B, Hang S, Zhang W, Mao C, Li D. An update on the bridging factors connecting autophagy and Nrf2 antioxidant pathway. *Front Cell Dev Biol*. 2023;11. doi:10.3389/fcell.2023.1232241

29. Abdul-Muneer PM. Nrf2 as a Potential Therapeutic Target for Traumatic Brain Injury. *J Integr*

Neurosci. 2023;22(4). doi:10.31083/j.jin2204081

30. Esteras N, Abramov AY. Nrf2 as a regulator of mitochondrial function: Energy metabolism and beyond. *Free Radic Biol Med*. 2022;189:136-153. doi:10.1016/j.freeradbiomed.2022.07.013

31. Tripathi S, Kharkwal G, Mishra R, Singh G. Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling in heavy metals-induced oxidative stress. *Heliyon*. 2024;10(18):e37545. doi:10.1016/j.heliyon.2024.e37545

32. Surai PF, Kochish II, Kidd MT. Redox Homeostasis in Poultry: Regulatory Roles of NF-κB. *Antioxidants*. 2021;10(2):186. doi:10.3390/antiox10020186

33. Pan YR, Hsieh YH, Wu TK, Chen HP. Mechanisms of antioxidative and anti-inflammatory treatments in chronic kidney disease and the potential benefits of hydrogen therapy: A narrative review. *Tungs' Med J*. 2025;19(Suppl 1):S16-S24. doi:10.4103/ETMJ.ETMJ-D-25-00005

34. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. Victor VM, ed. *Oxid Med Cell Longev*. 2017;2017(1). doi:10.1155/2017/8416763

35. El Ghouizi A, Ousaaid D, Laaroussi H, et al. *Ficus carica* (Linn.) Leaf and Bud Extracts and Their Combination Attenuates Type-1 Diabetes and Its Complications via the Inhibition of Oxidative Stress. *Foods*. 2023;12(4):759. doi:10.3390/foods12040759

36. De Bruno A, Mafrica R, Branca V, Piscopo A, Poiana M. Evaluation of Total Antioxidant Activity and Phenolic Profiles of Calabrian Breba Figs: A Detailed Study of Pulp and Skin from 29 *Ficus carica* L. Accessions. *Foods*. 2024;13(24):4035. doi:10.3390/foods13244035

37. Tkaczenko H, Kurhaluk N. Antioxidant-Rich Functional Foods and Exercise: Unlocking Metabolic Health Through Nrf2 and Related Pathways. *Int J Mol Sci*. 2025;26(3):1098. doi:10.3390/ijms26031098

38. Fu M, Yoon KS, Ha J, Kang I, Choe W. Crosstalk Between Antioxidants and Adipogenesis: Mechanistic Pathways and Their Roles in Metabolic Health. *Antioxidants*. 2025;14(2):203. doi:10.3390/antiox14020203

39. Yang B, Dong Y, Wang F, Zhang Y. Nanoformulations to Enhance the Bioavailability and Physiological Functions of Polyphenols. *Molecules*. 2020;25(20):4613. doi:10.3390/molecules25204613

40. Jalouli M, Rahman MA, Biswas P, et al. Targeting natural antioxidant polyphenols to protect neuroinflammation and neurodegenerative diseases: a comprehensive review. *Front Pharmacol*. 2025;16. doi:10.3389/fphar.2025.1492517