Journal of Zoonotic Diseases
https://jzd.tabrizu.ac.ir/
Published by the University of Tabriz
Online ISSN: 2717-2910

Targeting nuclear factor erythroid 2-related factor transcription factor/Hemoxygenase 1 (Nrf2//HO-1) antioxidant signaling pathway in *Brucella* infection

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Article type:
Mini review article

Keywords:
Brucella infection
Zoonosis
Signaling pathway
Oxidative stress

Article history:
Received:
January 14, 2025
Revised:
March 1, 2025
Accepted:
May 9, 2025
Available online:
May 10, 2025

Abstract

Human health is at serious risk from brucellosis, a zoonotic infection brought on by the genus *Brucella*, especially in areas where livestock is common. The clinical manifestations of brucellosis in humans are diverse, often beginning with nonspecific flu-like symptoms such as fever, chills, malaise, and arthralgia. The immune response to *Brucella* infection is complex, involving various cytokines and immune mediators, which can be influenced by the host's genetic background and environmental factors. Preventive measures primarily focus on livestock vaccination and public health education regarding the risks associated with unpasteurized dairy products and direct animal contact. The pathophysiology of *Brucella* is significantly influenced by oxidative stress, primarily in its interactions with the host immune system. It is known that *Brucella* species cause oxidative stress in their host cells, which activates a number of different biological processes, including the nuclear factor erythroid 2-related factor transcription factor (Nrf2) pathway. Nrf2 is a transcription factor that governs the expression of antioxidant proteins, which safeguard against oxidative damage caused by injury and inflammation. Activation of Nrf2 has been shown to upregulate HO-1, which is involved in modulating the immune response. The enzyme's activity regulates proinflammatory cytokines and anti-inflammatory environment, aiding *Brucella* in evading the host's immune defenses. Therefore, therapeutic strategies that enhance Nrf2 activation could improve the host's immune response while limiting the survival advantage of *Brucella*. Future research should continue to explore the therapeutic potential of targeting the Nrf2/HO-1 axis in various infectious diseases, particularly *Brucella* infection, to improve clinical outcomes.

Introduction

Brucellosis, a zoonotic infection caused by the genus *Brucella*, poses significant health risks to humans, particularly in regions where livestock is prevalent. The three species most frequently linked to human infections are *Brucella melitensis*, *Brucella suis*, and *Brucella abortus*. *B. melitensis* is the

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https://doi.org/10.22034/jzd.2025.19787
https://jzd.tabrizu.ac.ir/article_19787.html
Cite this article: Hosseini R. and Hajimohammadi A. Targeting nuclear factor erythroid 2-related factor transcription factor/Hemoxygenase 1 (Nrf2//HO-1) antioxidant signaling pathway in *Brucella* infection. Journal of Zoonotic Diseases, 2025, x-x

most dangerous and widely reported species worldwide (1, 2). Human infections typically arise from direct contact with infected animals or ingesting unpasteurized dairy products (3, 4). The clinical manifestations of brucellosis in humans are diverse, often beginning with nonspecific flu-like symptoms such as fever, chills, malaise, and arthralgia (5-7).

The disease can present acutely or chronically, with acute cases often characterized by undulating fever and systemic symptoms, In contrast, chronic cases may lead to severe complications such as endocarditis, osteomyelitis, and neurological disorders (8, 9). In particular, *Brucella canis*, while less common, has been associated with milder infections, yet it can still result in serious complications (10, 11). The variability in clinical presentation can complicate diagnosis, as symptoms may mimic other infectious diseases such as malaria or typhoid fever (12, 13).

Brucella's ability to survive and replicate within host macrophages contributes to its pathogenicity, allowing it to evade the immune response and establish chronic infections (14). Histological examinations of affected tissues often reveal myeloid cell infiltrates, indicating an inflammatory response, but brucellar arthritis typically does not lead to significant joint destruction (15). The immune response to *Brucella* infection is complex, involving various cytokines and immune mediators, which can be influenced by the host's genetic background and environmental factors (16).

Preventive measures primarily focus on livestock vaccination and public health education regarding the risks associated with unpasteurized dairy products and direct animal contact (8). Despite these efforts, brucellosis continues to pose a considerable public health challenge in various areas globally, especially in regions characterized by substantial livestock populations and insufficient veterinary health interventions (1, 2).

Treating brucellosis in humans is multifaceted, requiring a tailored approach based on the severity of the disease and the specific clinical scenario. The combination of doxycycline with rifampicin or streptomycin remains the gold standard, but in complicated cases, a more aggressive treatment strategy involving surgery and prolonged antibiotic therapy may be necessary to achieve successful outcomes (17, 18).

The importance of *Brucella* infection in veterinary medicine

The economic impact of brucellosis is profound, particularly in developing countries where it leads to reproductive failures in livestock, such as abortion and infertility, thereby affecting food security and livelihoods (19, 20). Domesticated animals, including sheep, cattle, goats, and pigs, are the primary reservoirs of *Brucella*, which can infect humans, particularly in rural settings where close contact occurs often (20, 21). Vaccination remains a crucial strategy in controlling brucellosis in veterinary settings. However, the effectiveness of available vaccines is usually debated. Some vaccines have been shown to provide inadequate protection, leading to a false sense of security among livestock owners and health officials (22, 23). For instance, low-performance vaccines can result in vaccinated animals still acting as reservoirs for the disease, complicating eradication efforts (22). Moreover, serological tests used for diagnosing brucellosis often fail to distinguish between vaccinated and infected animals, which may hamper the effective control of the disease. (24, 25).

The epidemiological landscape of brucellosis varies significantly across regions. In Uganda, studies have reported varying seroprevalence rates in livestock, indicating the complexity of brucellosis transmission dynamics (26, 27). Factors such as herd size, density, and vectors like ticks have been associated with increased prevalence (27, 28). In contrast, in regions with robust veterinary services, such as the United States, brucellosis has been eradicated mainly from domestic livestock through comprehensive vaccination and surveillance programs (29).

Multiple-locus variable number tandem repeat analysis (MLVA), one of the recent developments in molecular techniques, has improved our comprehension of the genetic diversity of *Brucella* strains and their epidemiological relationships (30, 31). These tools are invaluable for tracking outbreaks and informing control measures. Additionally, developing more specific serological tests, such as those targeting outer membrane proteins, holds promise for improving diagnostic accuracy and differentiating between vaccinated and infected animals (25, 32). According to the points mentioned above, brucellosis remains a critical concern in veterinary medicine, necessitating ongoing research and improved strategies for vaccination, diagnosis, and epidemiological monitoring. The integration of advanced molecular techniques and better vaccine formulations could significantly enhance control efforts, particularly in regions where the disease is endemic.

Role of oxidative stress in *Brucella* infection

A key element in the development of *Brucella* is oxidative stress, particularly due to its interactions with the host's immune system. *Brucella* species, such as *Brucella abortus*, have evolved strategies to endure and proliferate in the oxidative conditions present within host macrophages. The host immune response generates reactive oxygen species (ROS) such as superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) to combat intracellular pathogens, including *Brucella* (33). This oxidative stress is a critical factor that influences the survival and virulence of *Brucella*, as it must adapt to these hostile conditions to establish infection. Research indicates that *Brucella* can enter a viable but non-culturable (VBNC) state under oxidative stress conditions, which may contribute to its persistence in the host (34). Studies have shown that the presence of oxidative agents like H_2O_2 and iron (Fe^{2+}) leads to a rapid decline in colony-forming units (CFUs) while increasing ATP levels, suggesting a metabolic adaptation that allows *Brucella* to survive despite the oxidative challenge (34). Additionally, *Brucella*'s capacity to fight oxidative stress depends critically on the expression of antioxidant enzymes like catalase and superoxide dismutase (SOD). These enzymes help neutralize ROS, thereby enhancing the bacterium's survival within phagocytes (35, 36).

Brucella's ability to modulate the host immune response is also linked to its oxidative stress management. For instance, the thioredoxin-interacting protein (TXNIP) is upregulated during *Brucella* infection, which helps reduce nitric oxide (NO) and ROS production in macrophages, facilitating *Brucella*'s intracellular survival (37). Additionally, studies have indicated that the cold shock protein A (CspA) is induced under oxidative stress conditions, suggesting that *Brucella* can adapt its protein expression profile to cope with the hostile environment within macrophages (38).

The general stress response (GSR) system in *Brucella* is activated by oxidative stress, enabling the bacterium to regulate its virulence and adapt to the challenging intracellular environment (39, 40). This response includes the expression of various stress response proteins that assist in managing oxidative damage and promoting survival during infection (41).

Moreover, the interplay between oxidative stress and the immune response is complex. The release of proinflammatory cytokines in response to elevated oxidative stress may strengthen the immune response against *Brucella*, but it can also cause tissue damage. The balance between inflammation and oxidative stress is crucial for controlling *Brucella* infections, as excessive inflammation can hinder the host's ability to clear the pathogen effectively (42).

Nrf2 and HO-1 signaling pathway

A transcription factor called nuclear factor erythroid 2-related factor 2 (Nrf2) migrates to the nucleus in response to oxidative stress. It binds to the antioxidant response element (ARE) found in the promoter regions

of several genes, including Heme Oxygenase-1 (HO-1). This process plays a crucial part in cellular defense against oxidative damage by starting the transcription of many antioxidant genes. (43, 44). An enzyme called HO-1 is inducible and helps break down heme into biliverdin, carbon monoxide, and free iron—all vital for protecting cells from oxidative stress. (44, 45).

The Nrf2/HO-1 signaling pathway is recognized as a fundamental mechanism through which cells respond to oxidative stress. Studies have demonstrated, for example, that Nrf2 activation results in HO-1 upregulation, which ultimately has cytoprotective effects by lowering inflammation and oxidative damage. (46-48). This pathway has been implicated in various physiological and pathological contexts, including myocardial ischemia-reperfusion injury, where the activation of Nrf2 and subsequent HO-1 expression significantly mitigates oxidative stress-induced damage (47, 48). Furthermore, Nrf2's role extends beyond merely regulating HO-1; it also influences the expression of other antioxidant enzymes, enhancing the overall cellular antioxidant capacity (49, 50).

Research has demonstrated that the deficiency of Nrf2 exacerbates oxidative stress and related pathologies, such as cardiotoxicity induced by doxorubicin, highlighting its protective role (49, 51). Conversely, the induction of HO-1 has been shown to confer adaptive responses to oxidative insults, making it a potential therapeutic target in conditions characterized by oxidative stress (45, 51). For example, compounds like thymoquinone and mangiferin have been shown to activate the Nrf2/HO-1 pathway, leading to increased antioxidant defenses and reduced cellular damage in various models of oxidative stress (43, 44, 46).

Furthermore, the mitogen-activated protein kinase (MAPK) is a signaling pathway that affects the interaction between Nrf2 and HO-1. It can modify Nrf2 activity, affecting the expression of HO-1 (52, 53). This suggests that the regulation of the Nrf2/HO-1 axis is complex and involves multiple layers of signaling that respond to the cellular redox state.

Role of Nrf2 and HO-1 signaling pathway in Brucella infection

In specific infectious diseases, the Nrf2/HO-1 pathway has been implicated in various pathogens. For example, Brucella infection has been shown to induce HO-1 expression, which may facilitate the survival of the bacteria within host cells (54). Similarly, in viral infections such as Pseudorabies Virus (PRV), HO-1 induction has been associated with reduced viral replication, suggesting a protective role against viral pathogenesis (55). Moreover, increased HO-1 levels have been linked to the severity of COVID-19, implying that the Nrf2/HO-1 axis may be involved in the hyperinflammatory reactions seen in severe cases. (56, 57).

This cytoprotective mechanism is essential in preventing tissue damage during infections, as excessive oxidative stress can lead to cellular apoptosis and exacerbate inflammation (58, 59). Additionally, the modulation of the Nrf2/HO-1 pathway has been investigated as a potential therapeutic approach to strengthen the host's defense mechanisms against infections (60, 61).

Research indicates that *Brucella* infection triggers the expression of HO-1, a process significantly mediated by Nrf2 activation. For instance, Hu et al. demonstrated that *Brucella* induces HO-1 expression through signaling pathways involving AMPK, PI3K, and GSK3β, highlighting the importance of Nrf2 in this context (54). Oxidative stress-induced Nrf2 activation is crucial for HO-1 transcriptional activation, which alleviates oxidative damage and promotes cell survival during Brucella infection (54).

Nrf2 not only supports antioxidant defense but also regulates the inflammatory response. Nrf2 activation has been demonstrated to inhibit the production of proinflammatory cytokines, which is especially pertinent in the case of *Brucella* because the pathogen

can cause a strong inflammatory response that could lead to tissue damage (62). The anti-inflammatory properties of Nrf2 are facilitated by its capacity to suppress the NF-κB pathway, which is a crucial regulator of inflammation (63). Thus, Nrf2 serves as a dual protector against oxidative stress and inflammation during *Brucella* infections. The interplay between Nrf2 and other signaling pathways further complicates its role in *Brucella* pathogenesis. For example, the Keap1-Nrf2 system is a well-established regulatory mechanism where Keap1 acts as a negative regulator of Nrf2 under non-stressed conditions. Nrf2 is released from Keap1 in response to oxidative stress, moves to the nucleus, and starts the transcription of genes that produce antioxidants (64). Because it improves the cell's capacity to withstand the deleterious effects of reactive oxygen species (ROS) produced during the infection process, this mechanism is essential for the cellular response to oxidative stress caused by *Brucella* (64). Specifically, the production of CO has been recognized for its role in modulating inflammation and enhancing macrophage function, which is crucial during *Brucella* infection (65). Furthermore, research has shown that downregulating HO-1 expression can lead to increased susceptibility to infections and heightened inflammatory responses. For instance, the reduction of HO-1 in trophoblast giant cells during *Brucella* infection has been linked to increased cell death and adverse pregnancy outcomes, highlighting the protective role of HO-1 in maintaining cellular integrity during bacterial infections (66, 67). This implies that HO-1 is essential for the host's reaction to infection in addition to helping *Brucella* survive. HO-1 not only serves protective roles but also plays a significant part in regulating the immune response. The enzyme's activity has been associated with proinflammatory cytokines regulation and an anti-inflammatory environment promotion, which can be advantageous for *Brucella* as it seeks to evade the host's immune defenses (68). The interplay between HO-1 expression and the host's immune response underscores this enzyme's importance in *Brucella* infections. Understanding the role of HO-1 in *Brucella* pathogenesis could lead to novel strategies for managing brucellosis and improving outcomes in affected individuals.

Targeting the Nrf2/HO-1 Signaling Pathway therapeutically in cases of *Brucella* infection

The possibility of treating *Brucella* infections by altering the Nrf2 and HO-1 signaling pathways is becoming more widely acknowledged, considering how crucially these pathways control inflammation and oxidative stress. The Nrf2 pathway's activation raises the expression of HO-1, which has cytoprotective, anti-inflammatory, and antioxidant qualities (69-71). In the context of *Brucella* infections, studies have indicated that HO-1 expression is induced as a response to the infection, suggesting that *Brucella* may exploit this pathway to enhance its survival within host cells (54). This manipulation of the host's antioxidant defenses could facilitate *Brucella*'s intracellular replication and persistence. Moreover, the interaction between Nrf2 and HO-1 plays a vital role in regulating the immune response in the context of *Brucella* infections. Nrf2 activation has been linked to the control of several immune responses, such as the augmentation of phagocytic activity and the modification of proinflammatory cytokines (72, 73). This suggests that therapeutic strategies to enhance Nrf2 activity could bolster the host's immune response against *Brucella* by promoting HO-1 expression and thereby reducing oxidative stress and inflammation. Research has also highlighted the potential of various natural compounds to activate the Nrf2/HO-1 pathway, providing a promising avenue for therapeutic intervention. Compounds such as curcumin and dihydrolipoic acid have been shown to activate Nrf2, leading to increased HO-1 expression and subsequent protection against oxidative stress (56, 74). Moreover, the interplay

between Nrf2 and HO-1 is critical in regulating the immune response. HO-1 expression, for example, can affect the synthesis of proinflammatory cytokines like IFN-γ, which is necessary for macrophage activation and the bactericidal action against *Brucella* (75).

Furthermore, the use of antioxidants in therapeutic strategies against brucellosis has been explored. For instance, antioxidant administration could potentially enhance the efficacy of treatments for brucellosis by reducing oxidative stress levels in infected individuals (76, 77). This is supported by findings that show a significant increase in antioxidant levels following treatment in patients with brucellosis, indicating a depletion of the antioxidant system during the infection (78). These findings underscore the potential for developing Nrf2/HO-1-targeted therapies. By modulating these pathways, it may be possible to enhance the host's immune response against *Brucella*, reduce oxidative stress, and inhibit the pathogen's survival mechanisms. Future research should focus on developing specific Nrf2 activators or HO-1 inhibitors that can be effectively used with traditional antimicrobial therapies to improve outcomes in brucellosis treatment.

Conclusions

In conclusion, oxidative stress is a major factor in the development of *Brucella*, impacting both the host's immune response and the bacterium's survival strategies. *Brucella* has developed advanced strategies to combat oxidative stress, such as the synthesis of antioxidant enzymes and the adjustment of host immune responses, both of which are crucial for its survival and pathogenicity within the host. The Nrf2/HO-1 signaling pathway regulates inflammation and oxidative stress, crucial for mediating the immune response to infectious diseases. This pathway's initiation contributes significantly to the overall cytoprotective effects that are necessary for reducing tissue damage and controlling infections in addition to increasing HO-1 expression. Understanding these mechanisms in the context of disease management is even more crucial, given the possibility that antioxidant therapies could help treat brucellosis. Ongoing studies must focus on the therapeutic potential of influencing the Nrf2/HO-1 mechanism in several infectious diseases, to better the clinical outcomes.

Acknowledgements

Not applicable.

Ethical approval

Not applicable.

There were no ethical considerations to be considered in this research.

Conflict of interest

The authors declared no conflict of interest.

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