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The possible importance of the antioxidants and oxidative stress metabolism in the emerging monkeypox disease: An opinion paper

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Introduction

The world has been struggling with a major public health problem since December 2019: an infectious disease caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite vaccination, people are still infected and die because of COVID-19 since the virus mutates very quickly (1, 2). While the world is struggling with the COVID-19 pandemic, a new virus called Monkeypox (MPXV) alerts scientists about whether a new pandemic will arise. Monkeypox is a zoonotic, neglected, and emerging disease caused by the MPXV belonging to the *Orthopoxvirus* genus of the *Poxviridae* family. MPXV was first identified in Macaca irus wild monkeys in 1958 in Denmark; it was the first time specified in humans in 1970 in the Democratic Republic of the Congo in a 9-month-old boy (3, 4). However, several rodent species were also reported as reservoirs of this virus (5). Monkeypox disease has been reported as an emerging outbreak affecting 43 countries with 2103 confirmed cases (6).

The transmission ways of MPXV are direct contact with an infected animal or infected person *via* body fluids, using contaminated objects, and inhaling virus-containing respiratory droplets. The incubation time of the disease takes 5–21 days, where the symptoms of MPXV infection are reported as headache, fever, muscle pain, back pain, swollen lymph nodes, chills, adenopathy, maculopapular rash, especially on the palms, and exhaustion. Lesions such as macules, papules, vesicles, pustules, and scabs have been reported mainly in the palms of the hands and the soles of the feet. There is no treatment for MPXV infection; however, smallpox vaccination is considered a treatment option (7, 8). The MPXV infection begins like other viral infections with the entry of the virus into the cells and replication, leading to the immune response in the host cells, such as blocking the antiviral T-cell activation and inflammatory cytokine production. However, cellular mechanisms of MPXV infection, host cell interactions, immune responses, and destruction are not fully understood in humans despite animals (9).

Metabolism of virally infected cells

Viral infection and replication are tightly associated with the dysregulated immune system and inflammatory response. Since humans have complicated defense mechanisms against pathogens, viruses can quickly adapt to changing conditions such as the host's immune system and drug treatments. For instance, viruses deregulate cellular signaling pathways, including oxidative stress metabolism and cell death mechanisms, to escape the host's immune system (10, 11). The crucial step for virus replication is escaping from the cellular defense mechanism of the host cell (12, 13). Viruses are disparate from all living things; they don't inherently have their metabolism. Major cytosolic and mitochondrial metabolic pathways are altered in virus-infected cells (14, 15). Specific anabolic pathways such as glycolysis, glycogenolysis, pentose phosphate pathway (PPP), lipogenesis, cholesterol synthesis, one-carbon metabolism, and various transporters such as glucose and glutamine transporters are upregulated in virally infected cells (16, 17). It has also been investigated that the Warburg effect, which can be seen in cancer cells using glucose and producing lactate under normoxia conditions, can also be in the virus metabolism (18).

Importance of the antioxidant defense and antioxidant molecules in the viral infections

Various intrinsic and extrinsic factors regulate oxidative stress metabolism by balancing reactive oxygen species (ROS) and antioxidant capacity. Antioxidant metabolism is one of the major defense systems in many pathological conditions, including viral infections. PPP plays a vital role in antioxidant defense by regulating different enzymes. Glucose 6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the PPP involved in glutathione metabolism, antioxidant response, and bioenergetic and biosynthetic pathways (19–22).

The cytosolic hexokinase enzyme rapidly converts glucose to glucose-6-phosphate (G6P) to trap the glucose inside the cell by using an ATP molecule. This enzymatic reaction is not just specific to glucose; the hexokinase enzyme phosphorylates all the six-carbon sugars. After the phosphorylation of these sugar phosphates, many cellular conditions, such as hormones, energy status, infections, and all cellular signals, determine the fate of the phosphorylated molecule. It would enter breakdown or synthesis pathways according to the metabolic signals (23–30). G6PD enzyme is found in all cells and regulates the $NADP^+$/NADPH ratio involved in fatty acid, cholesterol, and neurotransmitter biosynthesis. Additionally, NADPH is the essential coenzyme in detoxification reactions *via* regulation of the balance between the oxidized glutathione (GSSG)/reduced glutathione (GSH) by involving in the glutathione reductase (GR)-catalyzed enzymatic and non-enzymatic reactions (31–34).

Furthermore, the reduced form of NADPH is also vital in cytochrome p450 superfamily-catalyzed reactions, such as cytochrome p450 monooxygenases and NADPH-cytochrome P450 reductase responsible for the xenobiotic detoxification, antioxidant-defense system, and cellular redox homeostasis. Since GSH/GSSG ratio is the major biomarker for oxidative stress, preserving the GSH pool is vital to maintaining antioxidant defense in the cell (35). Virus-infected cells also affect the mitochondrial pathways due to the high demand for biosynthetic processes such as the proliferation of virions. Mitochondria is the major source of ROS and enhanced ROS induces mitochondrial dysfunction leading to impaired electron transport chain (ETC) and energy metabolism (36). However, NADPH also protects mitochondria stress *via* a mitochondrial membrane from the effects of ROS *via* NADPH-dependent antioxidant enzymes (37). Human viral diseases, including COVID-19, increase the production of ROS and impair antioxidant mechanisms leading to the impairment of the immune system (38). On the other hand, virus-induced immune response contributes to oxidative stress as well, where oxidative stress increases inflammation, leading to enhanced oxidative stress as a vicious cycle (39). Danger signals trigger the immune system through pattern recognition receptors (PRRs) belonging to the Toll-like (TLRs) and the NOD-like (NLRs) families, where oxidative stress involves in these processes at several levels, including the release of danger molecules, activation by PRRs, and their downstream pathways (40). All viral infections cause redox imbalance in the host; for instance, prototypic poxvirus vaccinia virus (VACV) enhances ROS production at the side of the infection to promote viral replication. Additionally, high levels of ROS are required for VACV infection (41).

Antioxidant administration has been reported to ameliorate virus-induced side effects or to reduce viral replication yield, according to various studies. For instance, N-acetyl-L-cysteine (NAC) inhibits pro-inflammatory mediators in the alveolar cells infected with influenza virus A and B and with the respiratory syncytial virus (RSV) (42). The antioxidant molecule butylated hydroxyanisole (BHA) treatment ameliorates RSV-induced lung inflammation (43). Terameprocol (TMP) is a methylated derivative of nordihydroguaiaretic acid, which is a phenolic antioxidant derived from creosote bush. TMP showed antiviral and anti-inflammatory effects *via* potently inhibiting the growth of both cowpox virus and vaccinia virus *in vitro*, where TMP treatment effectively reduced the infectious virus yield (44). On the other hand, resveratrol altered genome replication and post-replicative gene expression of MXPV (45). Resveratrol (RV) is a natural polyphenol non-flavonoid compound found in grapes, berries, and several other plants. RV is accepted as one of the powerful polyphenols with many positive effects on metabolism and health and

significantly reduces the replication of MPXV (46, 47). No studies reveal the antioxidant's impact on the MPXV infection in humans since monkeypox is an emerging disease worldwide. Thus, the possible effect of the antioxidants on the MPXV infection in humans can be investigated to develop antioxidant-based therapeutic approaches to ease the severe symptoms.

Conclusion

All viruses depend entirely on the host's cell cellular metabolism, and every virus family has different molecular machinery to enter, using the host cells' energy and metabolic pathways multiplication and all steps in viral infection. However, we need novel studies to increase our knowledge on virus and virus-infected host cell metabolism, especially during the pandemic and the Monkeypox outbreak. Since antioxidants can reduce MPXV replication *in vitro*, according to the studies, antioxidant molecules can be investigated to develop therapeutic approaches or to ease the symptoms of MPXV infection.

Author contributions

DA and NU are responsible for the conceptualization and writing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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