

Divine life force: The fragile power of blood

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ABSTRACT

Issue 47–6 of the *Biomedical Journal* explores the delicate boundaries of human blood. It examines the relationship between anemia and the gut microbiome, as well as the modified activation patterns in compensatory blood oxygenation observed in COVID-19, and lastly a series of experiments investigates the effects of SARS-CoV-2 variant spike proteins on the biology and morphology of red blood cells. Additionally, a fungus endemic to Taiwan shows potential as a treatment for pulmonary fibrosis, while relevant co-infections in schistosomiasis appear to be benefitting from altered receptor signaling in macrophages. A genomic study identifies an important locus in Taiwanese patients with Tourette syndrome, and a retrospective evaluation is conducted on the incidental detection of common bile duct dilatation in pediatric patients.

1. Spotlight on reviews

Immortality at one's fingertips - who wouldn't dream of it? A fantasy for humans, a reality for the Greek gods and goddesses of Mount Olympus. The secret to eternal life was hidden in their ichor, the heavenly life force in their veins. The gods sustained their divine blood by consuming ambrosia and nectar, exclusive foods that maintained their immortality and powers. Without continued consumption, however, those abilities would fade. The colorless fluid ichor was believed to be fatal to humans, and consuming the gods' food was strictly forbidden, with severe punishment for transgressions. Yet, if a human managed to steal and eat ambrosia, they would gain immortality, just like the gods they revered. Theories about the composition of ambrosia and nectar suggest they may have included honey, olive oil, water, and other Mediterranean staples such as fruit, cheese, and pearl barley. Some ethnomycologists speculate that *Amanita muscaria* mushrooms may have been an ingredient contributing to the magic properties of ambrosia and nectar.¹⁻⁴

Honey, one of the world's oldest medicinal substances, has well-documented antimicrobial and wound-healing properties. It shows bactericidal and bacteriostatic effects, helps reduce the toxicity of mycotoxins, and enhances gut health by promoting beneficial bacteria like Bifidobacteria and Lactobacilli, especially when combined with probiotics [1–3]. Similarly, olive oil is known for its antimicrobial, antioxidant, and anti-inflammatory properties, owing to its phenolic compounds and fatty acids that modulate the immune system. Extra

virgin olive oil, in particular, alters the gut microbiome, reducing its diversity but shifting the microbial balance towards more protective bacterial populations [4–7].

The Mediterranean diet is rich in these foods and associated with favorable gut microbiome patterns linked to lower all-cause mortality [8–10]. Also, specific gut microbiota are correlated with healthy aging and extended longevity [11,12]. Cheese, another key Mediterranean food, has been suggested to lower levels of trimethylamine-N-oxide (TMAO), a gut microbiota-derived compound associated with cardiovascular disease [13]. Barley, a grain largely consumed in the ancient Mediterranean, reduces the risk of developing chronic disease, and contains phytochemicals with strong antioxidant and antiproliferative effects. Studies in mice indicate that barley consumption can change aging-related phenotypes, extend lifespan, as well as significantly alter the gut bacteria balance, thus promoting intestinal homeostasis [14–16].

Amanita muscaria, fly agaric, has been historically used for medicinal purposes and is known for its hallucinogenic and psychoactive properties [17]. Bringing those elements together, one could hypothesize that a small group of beings that lived secluded on a distant mountain, consuming foods that support a healthy and long life, but also being under regular influence of psychedelics could have created a god-like perception of immortality. The blood of those individuals, possibly laced with *Amanita muscaria*, might have been toxic to humans who lacked tolerance to the mushroom's effects.

The mythological idea of ichor as a partially toxic life force mirrors

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¹ <https://www.greeklegendsandmyths.com/ambrosia-and-nectar.html>, last access 10/20/2024.

² <https://greekgodsandgoddesses.net/myths/ichor/>, last access 10/20/2024.

³ <https://www.kurtvonmeier.com/amanita-muscaria-1>, last access 10/20/2024.

⁴ <https://www.math.uci.edu/~vbaranov/nicetexts/eng/mushrooms.html>, last access 10/20/2024.

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modern understanding of harmful microorganisms, bloodborne toxins and diseases. Blood, both literally and metaphorically, holds a unique place at the intersection of biology, culture, and spirituality - carrying life and disease, strength and vulnerability. An example reflecting the fragility of life, when the vital substance blood is imbalanced or compromised, is anemia.

Iron absorption, which is crucial to human health, occurs primarily in the gut. Certain pathogens can interfere with this process, competing with beneficial microbes for iron as well as potentially leading to a deficiency in the host. The battle for nutrients is part of a strategy called "nutritional immunity," where the host limits metal availability to prevent bacterial growth. Nutritional iron deficiency can lead to anemia, entailing disruption of the entire human organism. Microbial imbalances in the gut have been linked to various forms of anemia. In iron deficiency anemia (IDA) patients, restoring iron levels through supplementation has been shown to correct gut dysbiosis [18–20].

In this issue of the *Biomedical Journal*, Lerma et al. present a comprehensive study examining the relationship between IDA and gut microbiome changes in an animal model. They found that IDA negatively affected not only the microbiome and colonic metabolism but also weakened the intestinal barrier, leading to increased microbial translocation. *Clostridium* species became predominant, production of short-chain fatty acids increased, and bacterial load surged, highlighting the complex relationship between iron deficiency and gut health [Fig. 1] [21].

1.1. Blood dynamics in COVID-19

Another article of this issue of the *Biomedical Journal* looks into the body's mechanism to maintain tissue oxygenation when total body oxygen delivery is compromised as it is the case in COVID-19 infection. The hematological effects of SARS-CoV-2 play an important role in COVID-19 pathophysiology. Research indicates that SARS-CoV-2

exhibit dysregulation in red blood cell precursors, hemoglobin and iron metabolism, with Long-COVID patients showing compromised oxygen binding to hemoglobin [22,23].

Bertilacchi et al. investigated hypoxemia in COVID-19 cases with particular focus on factors influencing the hemoglobin saturation curve. Their findings reveal a modified activation pattern in compensatory blood oxygenation mechanisms, suggesting a distinct progression of COVID-19 [24].

2. Also in this issue

2.1. Original articles

2.1.1. From fairy rings to pharmacological frontiers

Humans have entertained close interactions with fungi for thousands of years. In folklore, fungi often inspired both wonder and fear. Fairy rings for instance were widely regarded as supernatural phenomena in Western and Northern Europe. These circular fungal formations were considered to be portals to realms inhabited by malevolent beings such as fairies, elves, witches, and other mystical entities. Entering a fairy ring was often thought to be dangerous for a human.⁵ Beyond folklore, mushrooms have long been valued on a global level for more than just nutrition. Given their extensive range of pharmacological activities, medicinal fungi are nowadays recognized for their beneficial potential as the future of health.⁶ Their spectrum of activity includes antiallergic, antibacterial, antifungal, anti-inflammatory, antioxidative, antiviral, cytotoxic, immunomodulatory, antidepressive, antihyperlipidemic, antidiabetic, digestive, hepatoprotective, neuroprotective, nephroprotective, osteoprotective, and hypotensive effects [25,26].

In related research, idiopathic pulmonary fibrosis remains primarily a diagnosis of exclusion within interstitial lung diseases, a category characterized by abnormal accumulations of inflammatory and mesenchymal cells [27]. Lan et al. investigated the potential of the fungus

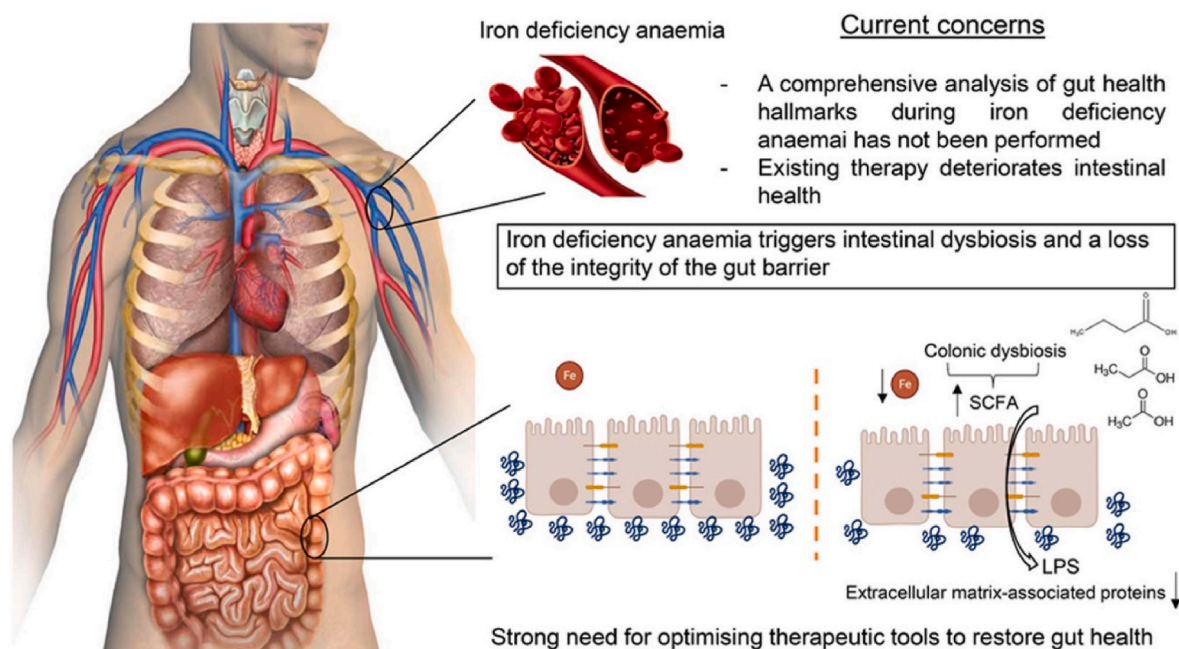


Fig. 1. According to Lerma et al. iron deficiency anemia not only causes intestinal dysbiosis, but also compromises gut barrier integrity and alters colonic metabolism [21].

frequently infects platelets and both platelet and erythroid precursors, altering their functionality. Following initial recovery, a subset of COVID-19 patients experiences persistent symptoms such as fatigue, shortness of breath, cough, and cognitive impairment. These cases

⁵ <https://gardencollage.com/inspire/wild-earth/myth-lore-fairy-ring/>, last access 10/23/2024.

⁶ <https://worldmushroomsociety.com/>, last access 10/23/2024.

Antrodia cinnamomea for treatment of pulmonary fibrosis. Their assays demonstrated that extracts from this fungus significantly protected mice from induced lung injuries and reduced the expression of inflammatory and fibrotic markers [28].

2.1.2. Purinergic cross-talk in parasite immunity

Purinergic signaling is integral to inflammatory processes, modulating immune responses against various bacterial and eukaryotic parasites. The P2X7 receptor and the NLRP3 inflammasome are implicated in the pathogenesis of numerous immune diseases. Notably, evidence suggests that purinergic signaling also plays a role in the morbidity associated with schistosomiasis, a neglected tropical disease caused by parasitic helminths. In schistosomiasis, macrophages are intensively recruited to infected organs. This chronic inflammatory, intravascular condition is tied to immune response polarization, influencing disease progression. Interestingly, schistosomes express certain enzymes of the purinergic system, possibly affecting host purinergic signaling pathways [29–31].

Having a closer look at the mechanisms behind impaired host immune defense, Thorstenberg et al. report that altered P2X7 receptor signaling in macrophages reduces their defensive role against *Leishmania amazonensis* during schistosomiasis. This might add to the disease's pathophysiology and facilitate clinically relevant co-infections [32].

2.1.3. WEIRD bias in tourette syndrome

Despite efforts to increase diversity in research, individuals of European ancestry remain significantly overrepresented, while ethnically diverse populations are largely excluded from human genomics studies. This exclusion not only hampers scientific progress but also creates an imbalance, limiting researchers' ability to accurately assess disease risks based on genetics and to develop new, potentially more effective treatments. The omission of genetic variants important for health and disease in a variety of populations may result in harmful consequences for disease prevention and treatment. Additionally, also non-genomic studies, such as psychological and behavioral research, are predominantly conducted in Western, educated, industrialized, rich, and democratic (WEIRD) societies, leading to implicit biases. These studies often assume minimal variation across human populations and establish misleading, generalized standard subjects.⁷

Previous reviews have explored the influence of environmental factors on the phenotypic expression of Tourette syndrome (TS) and highlighted the critical role of genetics in its etiology. TS, a neuropsychiatric disorder with complex inheritance, involves multiple genes and loci, and has been observed in children from various ethnic backgrounds [33,34]. Lin et al. present the first study on the genetic basis and risk factors of TS in Taiwanese patients, as previous genome-wide association studies (GWAS) were centered on Western groups. The research team identified a significant locus for TS associated with the *DRAM1*, a lysosomal transmembrane protein regulated by p53, which influences autophagy and apoptosis [35].

2.1.4. Wild methods in bile duct dilatation

During World War II (WWII), German forces developed retaliation weapons specifically designed for strategic and aerial bombardment of urban areas. The V1, a first-generation "buzz bomb", was a jet-engine powered, winged bomb named for the distinctive sound it produced.⁸ A recent study has revealed that exposure to bomb blasts are

closely correlated to concussion-like symptoms and physiological changes, including increased intestinal permeability (IP). Bacterial translocation into the bloodstream following blast exposure was observed and the presented symptom profile akin to mild traumatic brain injury, suggesting a link between IP and decreased cognitive function [36].

In WWII, bowel distention following bomb blasts became increasingly prevalent and was often fatal. British surgeon John Wild took a particular interest in improving treatment for patients with bowel injuries and developed an innovative method to measure bowel wall thickness in distended patients. Known as the "Wild tube," his technique employed noninvasive sonic energy to reflect echoes from soft tissues, enhancing the application of sound waves in medical diagnostics. Wild is recognized as the father of medical ultrasound.^{10,11}

With the widespread use of abdominal ultrasonography (US), the incidental detection of common bile duct (CBD) dilatation has become more frequent in pediatric patients. In a retrospective study, Su et al. reviewed the causes and clinical significance of CBD dilatation in asymptomatic pediatric patients, who typically show an uneventful clinical course [37].

2.2. Correspondence

2.2.1. Spike protein's grip on red blood cell morphology

Building on evidence indicating that SARS-CoV-2 affects the biology and morphology of blood cells, including erythrocytes, Dima, Salvagno, and Lippi conducted a series of experiments to explore the role of the SARS-CoV-2 spike protein in erythrocyte biology. Their findings revealed that, depending on the viral variant, the spike protein caused notable increases in mean corpuscular volume, alterations in red blood cell distribution width, and promoted hemagglutination. The team concluded that the Alpha and Delta variants exert the most pronounced effects on red blood cell morphology [38].

Disclaimer

None.

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

During the preparation of this work the author used ChatGPT Open AI in order to improve readability and language of the work. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing interest

The author declares no conflict of interests.

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¹⁰ <https://www.ob-ultrasound.net/jwildbio.html>, last access 10/24/2024.


¹¹ <https://www.washingtonpost.com/wp-dyn/content/article/2009/09/23/AR2009092304474.html>, last access 10/24/2024.

⁷ <https://www.sciencedaily.com/releases/2010/06/100630132850.htm>, last access 10/22/2024.

⁸ <https://www.iwm.org.uk/history/the-terrifying-german-revenge-weapons-of-the-second-world-war>, last access 10/23/2024.

⁹ <https://www.allworldwars.com/V-Weapons/20Crossbow/20Campaign.html>, last access 10/23/2024.

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