



Inherently imperfect, inherently evolving – The pursuit of precision through biomarkers

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ABSTRACT

Featuring a special section on cancer biomarkers, this issue of the *Biomedical Journal* highlights research on cfDNA, fecal miRNA, mitochondrial pathways, Epstein-Barr virus DNA, multi-biomarker panels combined with LC-MS-based methods, and circulating tumor cell (CTC) growth status as potential tools for cancer detection and management, including colorectal cancer, ovarian cancer, nasopharyngeal carcinoma, and hepatocellular carcinoma. Additionally, it explores the social stigma surrounding mpox, and discusses the achievements in miRNA research that earned the 2024 Nobel Prize in Physiology or Medicine. Advances in deep learning for trauma imaging are examined, alongside a review of decades of enterovirus research and current vaccination strategies. Other studies investigate the combined use of anthelmintic and antibiotic therapy for roundworm infection, and the application of a well-established Traditional Chinese Medicine herbal formula, commonly prescribed for gynecological conditions, against autoimmune hepatitis. Further articles elucidate the role of the nuclear receptor HNF4 in Schistosoma, mitochondrial dysfunction in acute kidney injury, the effects of astragalus polysaccharides on prostate cancer, and the use of deep learning to predict mortality from electrocardiograms.

1. Spotlight on reviews

After the decline of the Roman Empire, Spain experienced a highly transformative era under the 300 year long rule of Umayyad descendants. During this period, scientific knowledge, mathematics, architecture, and philosophy flourished. Central to this intellectual revival was the belief that human knowledge is inherently imperfect and must be continually advanced through research and experimentation. Drawing inspiration among others from Greek, Persian, and Indian sources, medieval Islamic scholars made a number of remarkable breakthroughs.¹²

One of the towering figures of this era was Abu Al-Qasim Al-Zahrawi, also known as Albucasis. Born in 936 AD near Cordoba, the capital of Al-Andalus, Al-Zahrawi is regarded as the father of operative surgery. His monumental 30-vol encyclopedia *Kitab Al-Tasrif* synthesized five decades of medical education, practice, and experience. Covering a broad range of fields including midwifery, pharmacology, dietetics, psychotherapy, therapeutics, and medical chemistry, it laid the groundwork for numerous medical disciplines, including urology, pediatrics, otolaryngology, ophthalmology, dentistry, cosmetology, and more.

Al-Zahrawi revolutionized surgery, introducing over 200 specialized tools tailored to specific procedures, including knives of various shape designed for precise incisions. He was the first to describe ectopic

pregnancy and identified the hereditary nature of hemophilia. His work was highly esteemed in the West, serving as the primary surgical reference in Europe for 500 years. Furthermore, Al-Zahrawi's emphasis on treating all patients, regardless of financial or social status, allowed him to observe and document a large spectrum of medical cases. He also asserted that surgeons must possess a deep understanding of anatomy and all branches of medicine, which was considered a radical notion for his time. One of Al-Zahrawi's innovations was the development of early diagnostic biopsies. He described the use of needle puncture to distinguish between types of goiter, a precursor to modern biopsy techniques [1–4].³⁴

Biopsies, critical for cancer diagnosis and other medical applications, have since evolved, including less invasive methods. Today, liquid biopsies (LBs) represent a groundbreaking advancement, enabling the collection of diagnostic information from fluids such as blood, urine, cerebrospinal fluid, pleural fluid, ascites fluid, or amniotic fluid. Liquid biopsies offer applications across various fields, including early cancer diagnosis, recurrence detection, treatment monitoring, drug selection, in cardiovascular disease, neurological disease organ transplant surveillance, and in reproductive medicine (Fig. 1). By analyzing components like circulating tumor DNA (ctDNA), circulating free DNA (cfDNA), circulating tumor cells (CTCs), cell-free fetal DNA (cffDNA), extracellular vesicles, microRNAs, and more, liquid biopsies provide

¹ <https://www.sjsu.edu/people/patricia.backer/history/islam.htm>, last access 01/25/2025.

² <https://archive.aramcoworld.com/issue/200703/rediscovering.arabic.science.htm>, last access 01/25/2025.

³ <https://www.frontiersin.org/news/2023/03/28/children-in-science-strongal-zahrawi-the-father-of-modern-surgery-strong>, last access 01/25/2025.

⁴ <https://www.embs.org/pulse/articles/could-al-zahrawi-be-considered-a-biomedical-engineer/>, last access 01/25/2025.

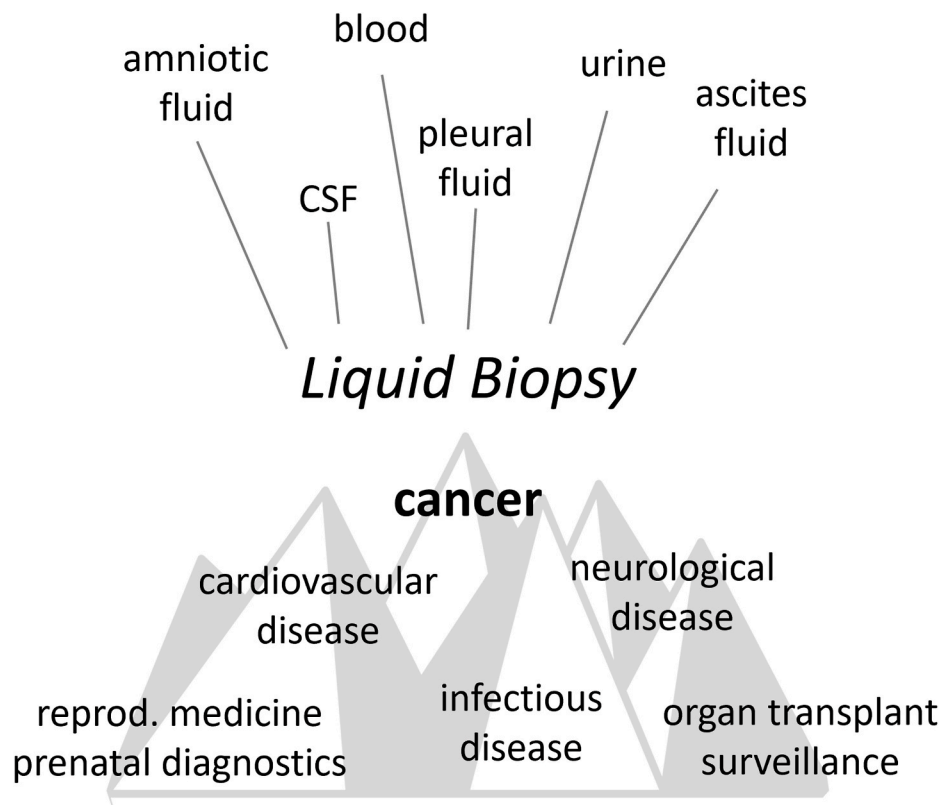


Fig. 1. Liquid biopsies, obtained from bodily fluids such as amniotic fluid, cerebrospinal fluid (CSF), blood, pleural fluid, urine, and ascites fluid, offer valuable insights with a wide range of medical applications. These include cancer diagnosis and monitoring, as well as applications in cardiovascular disease, infectious disease, neurological disorders, organ transplant surveillance, reproductive medicine and prenatal diagnostics.

insights into tumor staging, gene mutations, clonal evolution, and disease progression. This approach enhances patient outcomes by enabling personalized therapies and real-time monitoring while reducing the need for more invasive tissue biopsies [5–15].

LBs are poised to revolutionize medicine by offering a wealth of information while reducing invasiveness, highlighting the enduring legacy of diagnostic innovation inspired by pioneers like Al-Zahrawi. LBs hold immense promise for both fundamental cancer research and clinical applications. Emerging fields such as methylomics, fragmentomics, and nucleosomics are rapidly advancing, as they reveal features that can serve as precise tissue- and disease-specific fingerprints. For instance, the release of cfDNA is predominantly linked to cell death and turnover, while ctDNA provides deeper insights into tumor biology beyond mere tumor burden [16].

In this issue of the *Biomedical Journal*, Wong et al. highlight the latest advancements in LB technologies, focusing on epigenetic approaches that address challenges in cancer diagnosis, drug response prediction, and prognosis assessment. Aberrant DNA methylation patterns have been closely associated with cancer progression, offering potential diagnostic and prognostic biomarkers. Additionally, analyzing DNA fragmentation patterns can help estimate gene activity, further enhancing cancer detection methods. The study of nucleosome positioning and histone modifications through cfDNA sheds light on the chromatin landscape, enabling a deeper comprehension of the epigenetic mechanisms underlying cancer [17].

2. Also in this issue

2.1. Editorial

Chang and Ojcius introduce the six articles of this virtual special issue of the *Biomedical Journal* which explore various molecular cancer

markers identified over recent decades. Their summary outlines tumor-associated biomarkers, including those found within tumor cells, circulating biomarkers, and those secreted into the tumor microenvironment. Key considerations regarding the clinical utility of biomarkers are highlighted, such as the preference for non-invasive sample collection to enhance patient compliance and accessibility, the application of multi-omics approaches to address cancer heterogeneity, and the development of cost-effective, time-efficient models [18].

2.2. VSI: cancer biomarkers

2.2.1. Early warnings: fecal biomarkers transforming CRC detection

Colorectal cancer (CRC) was previously typically diagnosed after the age of 50 (late-onset CRC), but recent years have shown a troubling increase in early-onset CRC among younger individuals. An U.S. study revealed not only this demographic shift but also significant racial disparities, with Hispanic and African American populations disproportionately affected. These disparities are suggested to arise from epigenetic mechanisms influenced by environmental risk factors, including diet, stress, and alterations in the gut microbiome [19].

Detecting CRC early, especially through non-invasive methods, remains a challenge. Current diagnostic tools, such as the fecal immunochemical test (FIT), often produce false positives, leading to increased demand for colonoscopies, and limited sensitivity for early-stage disease. Addressing these limitations, Chen et al. previously developed a stool miRNA signature that may enhance the positive predictive value for CRC detection in FIT-positive populations [20]. In a subsequent review, Chen and Chang comprehensively summarize stool miRNA profiles and highlight emerging methods demonstrating the potential of fecal miRNAs as reliable biomarkers for early CRC detection [21].

2.2.2. An evolutionary partner offers insights into oncology

Throughout evolution, the destinies of mitochondria and eukaryotic cells have become deeply intertwined. This endosymbiotic relationship provides benefits to the host, yet mitochondria play complex roles in both health and disease. Beyond their well-known function for providing cellular energy, they participate in numerous mechanisms, including communication across physical systems. Notably, they are implicated in crosstalk between circadian clocks, the gut microbiota, and the immune system. Mitochondrial dysfunction has been linked to various conditions, including metabolic syndrome, neurological diseases, cancer, cardiovascular ailments, infectious diseases, and inflammatory disorders [22].

In ovarian cancer (OC), mitochondrial genes are involved in tumor metabolism. Analysis of mitochondrial gene expression through neural network algorithms offers potential for predicting prognosis and immunotherapy response in OC patients [23]. As the eighth leading cause of cancer-related death among women globally, OC presents significantly lower survival rates compared to other cancers.⁵

Faze et al. review mitochondrial dysfunction pathways as promising treatment targets and biomarkers for OC. The team demonstrates the altered mitochondrial function in cancer, such as changes in mitochondrial DNA, reactive oxygen species production, cellular dynamics, apoptosis, and autophagy [24].

2.2.3. A game changer in NPC

Epstein-Barr virus (EBV) is an oncogenic virus linked to multiple malignancies. Certain EBV-associated cancers, such as Burkitt lymphoma and nasopharyngeal carcinoma (NPC), are endemic in specific regions and exhibit a distinct geographic distribution, likely due to the global variation in EBV strains [25]. EBV infection may significantly elevate the risk of other diseases; for instance, the likelihood of developing multiple sclerosis rises over 30-fold following EBV infection, whereas individuals who have never been infected with EBV almost never develop the disease [26].⁶

Given the strong association between NPC and EBV, Hsu et al. reviewed emerging molecular diagnostic techniques for NPC, highlighting EBV-related biomarkers. These include EBV DNA detected in blood samples, viral latent transcripts and proteins, as well as EBV-specific antibodies. Additionally, EBV copy number serves as an indicator of viral reactivation and tumor burden, making these biomarkers valuable for both diagnosis and treatment monitoring in NPC patients [27].

2.2.4. Proteomics flexing its muscles against hepatocellular carcinoma

Recent discussions emphasize a transformative shift in hepatocellular carcinoma (HCC) treatment strategies, particularly through T-cell redirecting therapies. However, the current stage-linked treatment decision algorithm may result in undertreatment and suboptimal outcomes for patients with advanced-stage HCC, underscoring the overall need for refined therapeutic approaches [28]. Furthermore, currently only 20–30% of HCC patients are eligible for curative treatment, largely due to the absence of reliable tools for early detection and prognosis. Advances in liquid chromatography-mass spectrometry (LC-MS)-based proteomics have substantially contributed to identifying potential biomarkers emphasizing early diagnosis and prognostic assessment. In particular, single-cell proteomics has emerged as a powerful technique for uncovering cellular heterogeneity within tumors. Shin et al. project that multi-biomarker panels, combined with ongoing LC-MS advancements, will significantly enhance diagnostic precision and understanding of HCC pathogenesis, facilitating improved patient outcomes [29].

⁵ <https://worldovariancancercoalition.org/about-ovarian-cancer/key-stats/>, last access 01/28/2025.

⁶ <https://www.bbc.com/news/health-61042598>, last access 02/15/2025.

2.2.5. If you want to go fast

Go alone. If you want to go far, go together.⁷ Metastasis, a hallmark of invasive cancers, occurs when circulating tumor cells (CTCs) shed from a primary tumor site, entering the bloodstream. Isolating these cells has long been challenging due to their extreme rarity in peripheral blood samples and the lack of technologies capable of enriching them from specimens containing billions of blood cells. CTCs present as single cells or in multicellular clusters, which are further categorized into homotypic clusters composed solely of cancer cells, and heterotypic clusters that include stromal and immune cells [30]. In the case of CTCs, the cluster form - "going together" - offers distinct advantages that enhance metastatic potential. These include superior seeding capacity which increases metastatic efficiency [31,32], increased survival and proliferation due to sharing of resources and intracellular support [33], and resistance to treatment through unique gene expression profiles that enable the evasion of certain cancer therapies [34].

To address the challenge of CTC scarcity in the context of real-time monitoring, Chiang et al. conducted a prospective study validating an *ex vivo* culture protocol. This study successfully demonstrated a correlation between clinical response and CTC growth status across eight different cancer types, identifying a tool with potential to predict cancer progression [35].

2.3. Review articles

2.3.1. Navigating social stigma

Moclans are part of the diverse crew aboard *The Orville*, an exploratory spacecraft set 400 years into the future in a U.S. science fiction comedy-drama. This humanoid species is known for its heavily militarized industry, and exclusively consists of males in same sex partnerships. Moclan culture follows specific rituals, for instance Moclans urinate only once per year during their Great Release, an event celebrated together with friends and family. Their mating ritual involves one partner hunting and subduing the other, after which one of the partners lays and incubates an egg for 21 days. Occasionally, approximately once every 75 years according to the Moclan government, a female Moclan is born. However, by law, those newborns must immediately undergo corrective surgery to avoid being shunned by Moclan society. It is believed, that females are inherently unsuited both mentally and physically for the species' warrior culture. Ironically, it is later revealed that Moclus' most revered writer is a female who lives in hiding and publishes her works under a male pseudonym.⁸⁹¹⁰¹¹

Shifting focus to Earth and social stigmas affecting gay communities, the mpox outbreak in 2022 brought renewed attention to the intersection of healthcare and societal dynamics. Acharya et al. examined the complex web of risk factors, pathogenesis, treatment strategies, and social stigma associated with the monkeypox virus (MPV). The research team advocates for fostering inclusivity, education, and collaboration to replace stigma with empathy, mitigate risks through knowledge, and develop treatment approaches deeply informed by the lived experiences of affected communities [36].

2.3.2. The art of discreet influence

In 17th-century Renaissance Italy, women were bound by the rigid constraints of marriage laws and the burden of exorbitant dowries. Daughters were often bartered into unions designed to forge powerful

⁷ <https://andrewwhitby.com/2020/12/25/if-you-want-to-go-fast/>, last access 01/30/2025.

⁸ <https://medium.com/@guinevere42/the-morality-stories-of-the-orville-e-moclus-ethical-and-moral-issues-vs-practical-needs-f145876d87b9>, last access 01/19/2025.

⁹ <https://www.imdb.com/title/tt5691552/>, last access 01/19/2025.

¹⁰ <https://orville.fandom.com/wiki/Moclan>, last access 01/19/2025.

¹¹ <https://orville.fandom.com/wiki/Heveena>, last access 01/19/2025.

business alliances, their primary role reduced to producing heirs for their husband's lineage. With childbirth frequently proving fatal, men remarried often, usually favoring younger, more innocent brides. Divorce remained a privilege of wealthy men, leaving many wives with no recourse but to endure unchecked abuse under the absolute authority of their husbands. Amidst the shadowed streets of Sicily, then Naples, and finally Rome, a covert apothecary network emerged, centered around Giulia Tofana, a master in the art of crafting and packaging deadly poisons. Whispers claimed she inherited the recipe for her most lethal creation from her mother. The colorless, odorless Aqua Tofana circulated solely through word-of-mouth among women, discreetly concealed in innocuous-looking containers for face creams and beauty oils used by Italian women. Likely composed of lead, arsenic, and belladonna, its effects were insidiously gradual: the first dose induced weakness, the second brought stomach pain and vomiting, and by the third or fourth dose, death was inevitable with its cause misattributed to natural illness. It is said that over the span of 20 years in Rome alone, Tofana's handiwork led to the deaths of more than 600 men.¹²¹³¹⁴

In a different domain of silent yet profound influence, Ma et al. celebrate a groundbreaking discovery in molecular biology, earning the 2024 Nobel Prize in Physiology or Medicine. Celebrating how good things come in small packages, Ma et al. focus on the studies in *C. elegans* unveiling the vital role of microRNAs (miRNAs) in post-transcriptional gene regulation, which reshape our understanding of genetic control across species. These small RNA molecules act as master regulators, fine-tuning cellular pathways through gene silencing to safeguard physiological stability and prevent disease. Despite ongoing challenges, the therapeutic potential of miRNAs is vast. To fully harness their medical applications, innovative delivery mechanisms, such as lipid nanoparticles, are explored in order to protect these fragile molecules from degradation while ensuring precise, targeted treatment [37].

2.3.3. From chaos to clarity

The 1966 landmark report *Accidental Death and Disability: The Neglected Disease of Modern Society* sounded a call to action, urging for swift advancements in injury care. At the time, public indifference, the absence of 911 systems, and inadequate medical response compounded the crisis. Since then, significant strides have been made in establishing systems aimed at reducing injury-related morbidity and mortality.¹⁵

When a trauma patient arrives at the emergency department, immediate assessment is critical. The time-sensitive nature of these cases, coupled with limited information on the patient's injury mechanism or medical history, can heighten the challenge for providers.¹⁶ While some patients require emergent surgical intervention, advanced imaging modalities offer valuable diagnostic insights, enabling endovascular and non-operative management strategies. Deep learning (DL) is increasingly integrated into trauma imaging, enhancing computer-aided diagnostic tools. Its growing presence underscores its potential to improve efficiency and accuracy in trauma assessment. Chen et al. examined current DL applications in trauma imaging and explored future advancements, emphasizing the necessity of careful development and validation to ensure meaningful benefits for patient care [38].

¹² <https://www.syfy.com/syfy-wire/giulia-tofana-the-italian-serial-poisoner-who-became-a-legend>, last access 02/14/2025.

¹³ <https://aspectsofhistory.com/giulia-tofana-power-poison/>, last access 02/14/2025.

¹⁴ <https://www.historiamag.com/giulia-tofana-poisoner-murderer-saviour/>, last access 02/14/2025.

¹⁵ <https://www.ncbi.nlm.nih.gov/books/NBK230595/>, last access 02/21/2024.

¹⁶ <https://www.ncbi.nlm.nih.gov/books/NBK547757/>, last access 02/21/2025.

2.3.4. Got some guts: a quarter century of enterovirus research

Viruses are known to interfere with the secretion and content of extracellular vesicles, with notable parallels existing between these biological entities. The distinction between viruses and extracellular vesicles may be subtle, as they share several characteristics such as similar size, possession of a lipid bilayer embedded with cellular proteins, as well as utilization of the ESCRT machinery to leave from host cells. For example, Enterovirus A71 (EV-A71) has been found within small extracellular vesicles. This overlap complicates experimental protocols, as the techniques used to isolate viruses and EVs are largely comparable [39].

EV-A71 has become a significant public health concern in Asia-Pacific regions over recent decades. The virus causes severe central nervous system infections and neurological disorders that can be life-threatening [40]. Huang et al. provide an in-depth review covering of EV-A71 covering the molecular virology of EV-A71, its epidemiology, genetic recombination events, diagnostic criteria, treatment options, and prognosis. A major barrier to effective vaccine development is the genetic diversity of EV-A71, which results in variations in its surface proteins. This diversity requires a vaccine capable of neutralizing a wide range of viral variants. Additionally, the role of antibody-dependent enhancement in EV-A71 infections remains poorly understood, further complicating vaccine design efforts [41].

2.4. Original articles

2.4.1. Worms that make the world go round

Archaeoparasitology has become an invaluable tool for examining the interactions between past human populations, their environments, diets, and health. It proves particularly informative in cases where parasite traces endure while human or faunal remains and artifacts do not. The detection of parasites can also offer insights into the effectiveness of sanitation methods, cooking practices, lifestyles, and behaviors, as well as serve as markers for migration and trade routes. Ectoparasites, for example, may be found on preserved clothing, the hair of mummies, or within sediments from burial occupational layers. Intestinal parasites may be recovered from coprolites. Notably, before European invasion, roundworm and whipworm were not widespread in the Southwestern regions of North America. In Ancient China, where rice farming in paddy fields was practiced, and in Ancient Egypt, Nubia, and Mesopotamia with irrigation systems dependent on the Nile and Euphrates rivers, various strains of schistosomiasis were detected. Interestingly, some Neolithic and Bronze Age European populations, who built stilted settlements over lakes, appeared protected against whipworm and roundworm infections, as the eggs of these parasites cannot mature in water. However, those populations exhibited a higher prevalence of parasites transmitted through the consumption of raw fish and other freshwater foods [42,43].

Sofiyatun et al. conducted research on the effects of combined anthelmintic and antibiotic therapy during the early stages of *Angiostrongylus cantonensis* roundworm infection in mice. Their findings suggest that this innovative treatment effectively mitigates neurological damage in angiostrongyliasis patients, reducing brain damage and neurobehavioral impairments [44].

2.4.2. A pioneering herbal remedy from the medical sage of TCM

Zhang Zhongjing, often hailed as the medical sage of Traditional Chinese Medicine (TCM) and sometimes referred to as the "Chinese Hippocrates," practiced medicine in the early 3rd century CE. Motivated by compassion for those suffering amidst war and natural disasters, which had triggered widespread epidemics, Zhang made considerable contributions to the development of the six-stage pattern of cryopathology and the treatment of cold damage disorders. His work proved

particularly influential for its insights into typhoid and other febrile conditions [45].¹⁷ Zhang is credited with the earliest description of Guizhi Fuling Wan (GZFLW) in his seminal text *Treatise on Cold Damage Disorders*. This herbal formula, historically prescribed for various gynecological conditions, continues to be explored for its potential therapeutic applications, including the treatment of uterine fibroids, ovarian cancer, and polycystic ovary syndrome (PCOS) [46,47].¹⁸

Recent research by Kuo et al. extended the potential use of GZFLW to autoimmune hepatitis (AIH). In experimental studies on mice, oral administration of the formula significantly alleviated AIH and associated conditions, including hepatic apoptosis, inflammation, reactive oxygen species accumulation, functional impairment, and mortality [48].

2.4.3. From intestines to infestations: HNF4 in parasites

Hepatocyte nuclear factor 4-alpha (HNF4α) orchestrates complex transcriptional programs across multiple organs. This nuclear receptor (NR) is expressed in the liver, kidney, intestine, and pancreas. In the intestine, HNF4α governs processes such as maturation, differentiation, regeneration, and stem cell renewal. As a highly conserved transcription factor (TF), the diversity of its target genes arises from variations in chromatin looping, post-translational modifications, interactions with coregulators, and fluctuations in protein levels across different cell types and conditions. Like other members of the NR superfamily, HNF4α contains two highly conserved functional and structural domains: a DNA-binding domain (DBD) and a ligand-binding domain (LBD) [49, 50].

Schistosomes, the causative agents of the most significant helminthic disease in humans, exhibit an unusual reproductive biology. Unlike most hermaphroditic helminths, they are gonochoric, with distinct male and female individuals, and follow a monogamous mating system, a trait shared by only 1% of known species. Their sex ratio is male-biased [51].

Intrigued by the role of HNF4 in *Schistosoma japonicum* (SJHNF4), Wu et al. explored its expression and function. They found that SJHNF4 was expressed at higher levels in females than in males at both transcriptional and protein levels. Key functional domains of SJHNF4 were conserved, and its expression was localized primarily to the perithecium, reproductive system, and parts of the intestinal tissues in female worms. Additionally, SJHNF4 showed a strong correlation with essential metabolic pathways, including energy metabolism and nutrient absorption [52].

2.4.4. Mitochondrial protection in AKI

Olesoxime, a mitochondrial-targeted neuroprotective compound, interacts with outer mitochondrial membrane proteins, accumulates at the mitochondria, and prevents the opening of the permeability transition pore, which is influenced by factors such as oxidative stress (OS) [53]. The kidney is highly susceptible to OS, a key pathogenic factor in cellular damage that contributes to the initiation, progression, and development of acute kidney injury (AKI). Both AKI and chronic kidney diseases can arise from dysregulated OS responses, inflammation, and apoptosis [54]. In an effort to address mitochondrial dysfunction in AKI, Wang et al. investigated olesoxime in an AKI mouse model. Their findings revealed that olesoxime significantly reduced cisplatin-induced nephrotoxicity, apoptosis, inflammation, and OS in the kidneys of AKI mice, suggesting its potential capacity for alleviating mitochondrial dysfunction [55].

2.4.5. A timeless remedy with modern insights

The dried root of *Astragalus* has been a cornerstone of traditional

herbal medicine in China and other Asian countries for over 2000 years. *Astragalus* is valued for its diverse biological activities and pharmacological effects, as well as recognized for its hepatoprotective, tonic, expectorant, and diuretic properties. *Astragalus polysaccharide* (APS), one of its key bioactive components, exhibits a broad spectrum of pharmacological activities, including hepatoprotection, immunomodulation, anticancer, antidiabetic, antiviral, anti-inflammatory, antioxidant, and cardiovascular protective effects [56].¹⁹ During previous SARS-CoV outbreaks, several Chinese provinces implemented Traditional Chinese Medicine (TCM) strategies based on principles such as tonifying qi, defending against external pathogens, dispelling wind, clearing heat, and resolving dampness. *Radix Astragali* was among the most frequently utilized herbs in these treatments [57].

In their study, Wu et al. assessed the effects of APS on prostate cancer, revealing that lower concentrations promoted CD8⁺ T cell proliferation, while higher concentrations activated both CD4⁺ and CD8⁺ T cells. Additionally, APS influenced immune responses by modulating the programmed death-ligand immune checkpoint pathway [58].

2.4.6. Predicting mortality

In 2025, two partial solar eclipses will occur²⁰, phenomena that, in ancient times, were often perceived as harbingers of catastrophe. A solar eclipse was usually tied to apocalyptic prophecies or interpreted as divine displeasure. Such was their significance that they could even bring wars to a halt. Yet, many ancient civilizations, including those of China, Mesoamerica, Ancient Greece, and Mesopotamia, developed methods to predict these celestial events with remarkable accuracy. In response, specific rituals were performed. In Assyria, for instance, a solar eclipse was considered an ominous sign foretelling the death of the king. To counteract this perceived threat, a temporary ruler, a one-day decoy king, was crowned, while the true king remained in hiding. Once the eclipse had passed, however, the unfortunate stand-in was typically executed.²¹

Lin et al. leveraged deep learning to predict one-year mortality from electrocardiograms (ECGs). Their research introduced ECG-Surv, a novel deep neural network designed specifically for survival analysis. This model effectively harnessed ECG data, surpassing traditional statistical methods in predicting one-year all-cause mortality and cardiovascular death [59].

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.

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¹⁹ <https://pubmed.ncbi.nlm.nih.gov/32186034/>, last access 02/21/2025.

²⁰ <https://www.britannica.com/topic/Eclipses-in-2024-2025-and-2026>, last access 02/21/2025.

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