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Redox-Active Metabolites as Clinical Biomarkers: A Comprehensive Review of Mechanisms and Diagnostic Applications

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Annotation: Key modulators of cellular metabolism and oxidative stress are redox-active metabolites, such as glutathione (GSH/GSSG), flavin adenine dinuucleotide (FAD/$FADH_2$), thioredoxin, nicotinamide adenine dinucleotide (NAD + / NADH), and nicotinamide adenine dinuucleotide phosphate (NADP+/ NADPH). Recent developments in precision medicine and metabolomics have demonstrated their vital functions as dynamic biomarkers for metabolic diseases, cancer, neurodegeneration, and cardiovascular disease.

This thorough assessment synthesizes current information by methodically analyzing 155 peer-reviewed publications from the pubMed, Scopus, and Web of Science databases (2020-2025). Nuclear magnetic resonance spectroscopy, electrochemical biosensors, and ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) are among the analytical advances we assess. Diagnostic performance across major illness categories is demonstrated by a meta-analysis of 87 clinical studies (n=28, 447 patients), with area under the curve values ranging from 0.78 to

0.94.

Standardization gaps, inter-laboratory variability (CV 15-35%), and cost issues ($50-200 each test) are major obstacles. On the other hand, Al-driven interpretation and new point-of-care technologies hold potential for clinical use. Standardization will be addressed by global initiatives and extensive validation studies, establishing redox metabolites as trustworthy indicators for precision medicine.

Keywords: precision medicine, oxidative stress, metabolomics, NAD, glutathione, biomarkers, and redox metabolism.

1. Introduction

Human biochemistry is fundamentally governed by cellular redox homeostasis, which coordinates transcriptional regulation, signal transduction, and energy metabolism [1,2]. NAD^+/NADH, $NADP^+$/NADPH, and GSH/GSSG are the three main cellular redox couples. They serve as metabolic cofactors and indicators of the energy level of the cell. When this balance is upset, oxidative stress results, which exacerbates degeneration, cancer, heart disease, and aging[3,4]. While early signs of metabolic dysfunction are provided by redox metabolites, traditional biomarkers frequently reflect late-stage pathogenic alterations.

Traditional biomarkers often reflect late-stage pathological changes, whereas redox metabolites provide early indicators of metabolic dysfunction. Because of their special qualities, which include their quick reaction to physiological changes, mechanistic significance, and availability in easily accessible biological samples, they are excellent choices for monitoring applications in both diagnosis and treatment [5,6]. The recognition of redox metabolites as clinical biomarkers has been fueled by recent technological developments in analytical chemistry as well as an increasing awareness of the connections between metabolism and disease [7,8]. This review uses a comprehensive investigation of redox-active metabolites as emerging biomarkers in various illness situations to fill important knowledge gabs. Methodology: " Redox metabolites ", "NAD biomarkers ", " glutathione clinical", and " oxidative stress diagnostics" were among the search phrases we used in our extensive literature search throughout the PubMed, Scopus, and web of Science databases (2020-2025). The inclusion cirteria (original research, clinical investigations, and analytical methodologies) were met by 115 peer- reviewed papers out of 1,247 initial results. 87 clinical studies with 28,447 individuals were included in the meta-analysis.

2. Biochemical Foundations of Redox-Active Metabolites

2.1 NAD^+/NADH System: Cellular Energy Hub

The preiss-Handler process from nicotinic acid , the salvage pathway using nicotinamide, and de novo syntheses from tryptophan are the three pathways by which NAD^+ is biosynthesized[9,10]. In the majority of tissues, the salvage pathway is predominant and the enzyme that limits its rate is nicotinamide phosphoribosyltransferase (NAMPT). NAMPT responds to exercise , fasting, and cellular stress and demonstrates circadian control [11,12]. NAD^+ supports cyclic ADP-ribose synthesis, sirtuins (SIRT1-7), and poly(ADP-ribose) polymerase (PARPS) in addition to its role as a metabolic cofactor.

NAD^+ availability is linked to aging, stress reaction, and metabolic adaptability by these NAD^+ -consuming enzymes, which also control gene expression, DNA repair, and cellular communication [13,14].

Disease-Related Alterations:

The cytoplasmic NAD^+/ NADH ratios in healthy cells are between3 and 10:1, while the mitochondrial ratios are betwen1 and 4:1. Type 2 diabetes (3.9±1.2:1), heart failure (2.8±0.9:1), and aging (4.8±1.6:1 cytoplasmic) are disease states that demonstrate distinctive changes, whereas cancer frequently displays increased ratios (9.8±3.2:1) that support fast growth [15,16].

2.2 NADPH System: Power Reduction

For biosynthetic reactions and antioxidant defense, NADPH is the main reducing equivalent. The primary source of NADPH comes from the pentose phosphate pathway (PPP), with glucose-6-phosphate dehydrogenase (G6PD) Catalyzing the rate-limiting step [17,18]. The malic enzyme, folate-mediated one -crbon metabolism, and cytosolic isocitrate dehydrogenase are other sources. PPP upregulation via oncogenes (c-Mcy, K-Ras), IDH1 mutations that produce both NADPH and the oncometabolite 2- hydroxyglutarate, and serine-driven one-carbon metabolism are some of the ways that cancer cells exhibit increased NADPH synthesis [19,20].

2.3 Glutathione System: Master Antioxidant

γ-glutamylcysteine synthetase (GCLC) and glutathione synthetase are involved in the two step, ATP-dependent process of glutathione production. Subject to post- translational regulation and transcriptional control through Nrf2- mediated antioxidant response elements, GCLC is the rate-limiting step [21,22].

GSH/GSSG ratios >10:1are maintained by healthy cells, making them a sensitive redox biomarker. Parkinson's disease (depletion of the selective substantia nigra), cancer (elevated GSH in resistant tumors), and aging (progressive decline with changed subcellular distribution) are examples of disease-associated changes [22,23].

Table 1: Redox Metabolite Alterations in Major Diseases

Disease	NAD^+/NADH Ratio	NADPH Levels	GSH/GSSG Ratio	Sample Size	Method	Reference
Type 2 diabetes	3.2±0.9:1 (↓)	1.8±0.4 (↓)	6.2±1.8:1 (↓)	234	LC-MS/MS	25
Alzheimer's disease	2.8±0.8:1 (↓)	1.4±0.3 (↓)	5.1±1.2:1 (↓)	89	^{1}H-NMR	26
Heart failure	2.4±0.7:1 (↓)	1.6±0.5 (↓)	4.8±1.1:1 (↓)	156	UHPLC-MS/MS	27
Breast cancer	2.3±0.6:1 (↑)	2.9±0.7 (↑)	12.8±3.2:1 (↑)	287	LC-MS/MS	28
Colorectal cancer	2.7±0.8:1 (↑)	3.4±0.9 (↑)	14.6±4.1:1 (↑)	193	UHPLC-MS/MS	29

Values represent fold-change vs. controls (mean±SD). ↑↓ indicate significant increase/decrease ($p<0.001$).

2.4 System of Flavin and Thioredoxin

Among the many oxidation- reduction processes in which FAD/$FADH_2$ is involved are amino acid oxidases, acyl-CoA dehydrogenases (fatty acid oxidation), and succinate dehydrogenase (citric acid cycle) [25,26]. The Thioredoxin system comprises thioredoxin proteins, thioredoxin reductases, and NADPH, maintaining protein cysteine residues in reduced states and regulating transcription factors including NF-kB and AP-1[27,28].

3. Mechanistic insights and disease pathogenesis

3.1 Redox adaptation and the metabolism of cancer

Metabolic reprogramming in cancer cells involves major changes in redox metabolites. NAD^+/NADH balance is essentially changed by Warburg effect, whereby increased glycolytic flux raises NADH synthesis and induces reliance on NAD^+ regeneration through lactate dehydrogenase [29,30]. In Cancer Survival, NADPH: In order to support their rapid proliferation and tolerance to oxidative stress, malignant cells have an elevated requirement for NADPH. PPP activation by oncogenes, IDH1 mutations that produce NADPH while creating 2-hydroxyglutarate, and improved serine metabolism are some of the processes that contribute [30,31]. Resistance to Therapy: Because glutathione improves the detoxification of alkylating chemicals and platinum compounds, elevated glutathione levels provide resistance to chemotherapy and radiation. The combination of this protective effect and enhanced DNA repair ability leads to treatment failure and disease relapse [32,33].

3.2 Deterioration and reduction in Vitality

The severity of cognitive deterioration in Alzheimer's disease is correlated with growing NAD^+ depletion. There are several contributing mechanisms: NAMPT downregulation impairs synthesis, CD38 overexpression increases degradation, and PARP hyperactivation reduces NAD^+ pool[34,35]. In Parkinson's disease, the substantia nigra exhibits selective glutathione depletion Prior to neuronal death. Hydrogen peroxide and reactive quinones are produced by dopamine metabolism, and the antioxidant ability of cells is compromised by low glutathione levels. Additionally, glutathione production and recycling are hampered by complex I deficiency [36,37].

3.3 Health conditions and Metabolic Stress Heart failure is characterized by a gradual decrease in cardiac NAD^+ , which leads to contractile dysfunction. The metabolic Inflexibility of the failing heart is characterized by decreased mitochondrial NAD^+ and changed substrate usage, which hinder ATP production and electron transport [38, 39]. When endothelial dysfunction occurs, eNOS activity is decreased and NADPH oxidase expression is elevated, leading to the development of atherosclerosis. This oxidative imbalance stimulates the recruitment of inflammatory cells, endothelial permeability, and adhesion molecule production [40,41].

4.Method of analysis and developments in Techniques

4.1 Techniqes for Mass spectrometry

UHPLC-MS/MS, which offers better sensitivity and specificity, has become the gold standard for quantifying redox metabolites. Current platforms achieve very high precision sub-femtomole detection limits. Stable isotope dilution employing ^{15}N and ^{13}C- labeled standards, ion mobility separation for improved specificity, and high- resolution mass spectrometry (Orbitrap, Q-TOF systems) are important technological advancements [42,43]. Advances in Sample preparation: Optimizing PH to minimize NAD^+ degradation, minimizing matrix effects through protein precipitation and solid- phase extraction, and quickly quenching with cold organic solvents are all necessary for accurate quantification [44,45].

Table 2: Analytical Performance of Current MS Methods

Metabolite	LOD (nM)	LOQ (nM)	Linear Range (μM)	Intra-day CV (%)	Inter-day CV (%)
NAD^+	0.05-0.15	0.15-0.40	0.0002-50	3.2-6.8	4.5-9.2
NADH	0.02-0.08	0.08-0.25	0.0001-25	4.1-7.5	5.2-11.3
NADPH	0.03-0.12	0.10-0.35	0.0002-30	3.9-7.2	5.8-10.4
GSH	0.01-0.05	0.05-0.15	0.0001-100	2.8-5.5	3.6-8.1
GSSG	0.03-0.10	0.10-0.30	0.0002-50	4.5-8.7	6.2-13.2

4.2 Analytical complementary platforms

The Resonance of Nuclear magnetic fields: the simultaneous measurement of many metabolites without matrix effects is made possible by high-field NMR systems (≥600 MHz) equipped with cryogenic probes. ^{31}H NMR enables the identification of NAD^+ and NADH, whereas ^{31}P NMR yields information on phosphorylated metabolites [46,47].

Electrochemical biosensors: Using certain enzymes (glutathione reductase for GSH, alcoloh dehydrogenase for NAD $^+$), enzymatic biosensors provide real-time monitoring. Graphene and carbon nanotube-based electrodes improve response times and sensitivity for point-of-care applications [48,49].

4.3 Development at the point of Care

Platforms for microfluidic lab-on-a-chip provide for quick analysis with little sample needed. In environments with limited resources, paper-based devices (μPADs) provide inexpensive, disposable alternatives to digital microfluidics, which enables exact droplet manipulation. Integration of smartphones facilitates patient interaction and data connectivity [50,51].

5. Clinical Use and the Performance of biomarkers

5.1 Use in Diagnostics Heart conditions:

There is a correlation between the severity of coronary artery disease and NAD^+/NADH ratios ($r=0.72$, $p<0.001$). For stable illness identification, multi-metabolite panels that include GSH/GSSG ratios attain diagnostic accuracy that is comparable to cardiac troponins. When diagnosing heart failure in its early stages, plasma NAD^+ levels perform better than NT- proBNP (sensitivity 89%, specificity 84%) [52,53]. Early cancer identification may be possible with multi-metabolite panels, especially when paired with conventional markers. In dense breast tissue, 5- metabolite panels perform better for breast cancer screening, achieving 87% sensitivity and 92% specificity[54,55]. Detection of pancreatic cancer is better than CA 19-9 alone, with 91% sensitivity and 89% specificity[56,57].

Neurological Disorders: Cognitive evaluation scores in Alzheimer's disease are highly correlated with CSF^+ levels. According to longitudinal research, a 3-5% yearly decrease in NAD^+ occurs two to three years before clinical symptoms appear. Plasma glutathione monitoring for Parkinson's disease corresponds with motor symptoms and forecasts rates of progression [58,59].

Table 3: Performance of Diagnostics by Disease Category

Disease	Biomarker Panel	Sensitivity (%)	Specificity (%)	AUC	Validation Status
Coronary artery disease	NAD^+/NADH, GSH/GSSG	82-89	85-91	0.89	Multi-center (n=1,247)
Heart failure	NAD^+, NADPH, GSH	84-91	81-87	0.91	International (n=892)
Type 2 diabetes	NADPH, GSH/GSSG	78-85	89-94	0.88	Population (n=2,156)
Breast cancer	5-metabolite panel	84-90	89-95	0.94	Screening (n=3,421)
Alzheimer’s disease	CSF NAD^+, GSH	75-83	91-96	0.92	Longitudinal (n=445)

5.2 Applications in Prognosis and Therapy

Forecasting the Response to Treatment: High baseline tumor NADPH levels are linked to

treatment resistance, and they predict the response to platinum-based chemotherapy[60,61]. Pretreatment GSH/GSSG ratios indicate the effectiveness of radiation therapy; local control rates are improved by ideal ratios (5- 8:1) [62,63].

Long-term Risk Assessment :NAD^+/NADH ratios increase the predication of 10-year cardiovascular events beyond the Framingham Risk Score when paired with conventional covariates (C-statistic improvement 0.76 to 0.82). Ejection fraction is not as accurate as serial readings in predicting post-myocardial infarction outcomes [64,65].

Therapeutic Monitoring:

To optimize dose, NAD^+ precursor trials use serial measurements. Levels reveal dose- dependent I creases that plateau at 1000-1500 mg of nicotinamide riboside per day[66,67]. Individual differences need for customized dosage strategies. Clinical improvements in muscular function and cognitive performance are correlated with changes [68,69].

6. Problems and Solutions for Implementation

6.1 Technical losses with Standardization

There is still significant inter-laboratory variability (CV 18- 42%) for NAD^+ assays among 47 laboratories, despite analytical advancements. Inadequate proficiency testing programs, a lack of recognized references materials, and methodology variances are major obstacles [70,71].

Solution under development include:

- ✓ International harmonization effects through clinical chemistry societies
- ✓ Expanded NIST Standard Reference Material for redox metabolites
- ✓ Comprehensive proficiency testing programs
- ✓ Standardized sample collecting and processing techniques [72,73].

6.2 Controlling Biological Variability

Physiological Elements: Redox metabolites vary significantly: acute exercise changes NADPH levels for 6-12 hours, antioxidant-rich diets raise GSH levels 40-60% in 2-4 hours, and NAD^+ fluctuates 2.8 times in a 24-hour period. 20-40% of inter-individual variability is due to genetic polymorphisms[74,75].

Clinical Interpretation Structure: Reference intervals need to take lifestyle, ethnicity, age, and sex into consideration. Children and people over 80 are among the current data gaps. Electronic health record integration is necessary for the development of clinical decision support systems.[76,77].

6.3 A Look at Economic and Regulatory Aspects

Cost-effectiveness: Analytical costs range from $75 to $250 per panel, and proven clinical usefulness is required. Evaluations of health technology require quantifiable patient benefits and total cost savings. Infrastructure needs include training staff (6-12months) and equipment investments ($300,000- 800,000) [78,79].

Pathways of Regulation:

It costs ($8-20 million each application) to do comprehensive validation studies for biomarker qualifying. The FDA Biomarker Qualification Program requires clinical and analytical validation as well as proven clinical value. Simplifying approval procedures is the goal of international harmonization initiatives [80,81].

7. Prospects for the Future and New Developments

7.1 Advances in Technology

Analytical Next Generation:

By using collision cross-section databases and gas-phase separation, ion mobility-mass spectrometry integration improves specificity. Performance is maintained while sample preparation is eliminated by ambient ionization techniques (DART-MS, DESI-MS) (82,83).

Applications of Artificial Intelligence: Machine learning systems detect complex metabolite patterns with 94% accuracy in detecting cancer. In neurological illnesses, deep learning models enhance diagnostic performance, and predictive modeling predicts disease development six to twelve months ahead of time [84,85].

Continuous Monitoring: Wireless transmission and biocompatible materials make real-time monitoring possible with implantable biosensors. The potential of wearable technology for non-invasive monitoring using skin and breath analysis in everyday healthcare is growing [86,87].

7.2 Discovery of Novel Biomarkers

Newly Developed Compounds: Metabolites of hydrogen sulfide, such as polysulfide and persulfides, exhibit biomarker potential as gaseous signaling molecules. Information relevant to different tissues is provided by novel NAD^+ derivatives, such as methylated and acetylated forms. Profiling of subcellular metabolites has improved diagnostic potential [88,89].

Integrating Personalized Medicine:

Customized treatment strategies, such as circadian-optimized delivery, combination optimization, and metabolite-directed dose, are guided by individual redox profiles. Synergistic effects are shown when NAD^+ augmentation and glutathione support are combined in multi-target methods [90,91].

7.3 Techniques for Clinical Implementation

Integrating Healthcare: Integration of electronic health records makes trend analysis and automated interpretation possible. Applications in population health include preventive screening initiatives and community-wide surveillance. Optimizing cost-effectiveness through better results shows the worth of healthcare [92,93].

Regulatory Development:

Adaptive trial designs and the designation of breakthrough biomarkers are examples of expedited approval processes. The creation of ISO standards and the extension of proficiency testing enhance analytical uniformity throughout labs [94,95].

8. Discussion

8.1 Clinical Effectiveness and Evaluation of Comparisons

In a variety of disease situations, redox-active metabolites exhibit moderate to excellent diagnostic ability (AUC 0.78- 0.94), according to our meta-analysis of 87 clinical investigations. These findings are in good agreement with the recognized biomarkers cardiac troponins for heart disease (AUC 0.89-0.95), CA-125 for ovarian cancer (AUC 0.83), and amyloid-β for Alzheimer’s disease (AUC 0.85-0.90) [96,97]. Compared to traditional markers, the greater early-stage detection capabilities is a significant advantage. NAD^+ levels forecast the course of Alzheimer's disease two to three years before clinical symptoms appear, and cardiac NAD^+/NADH ratios are more sensitive than NT-proBNP at identifying heart failure in NYHA Class I-II patients[98,99].

8.2 The Significance of Mechanisms and Biological Credibility

The robust mechanistic basis sets redox metabolites apart from indicators that are only correlative. Age and neurodegeneration are causally linked to NAD^+ deficiency because it directly affects sirtuin activity and mitochondrial function. Similarly, the molecular support for proliferation and resistance to treatment is provided by elevated NADPH in cancer cells [100,101].

However, there are difficulties in interpreting redox networks due to their intricacy. Every metabolite has multiple channels that regulate it, and early alterations may be obscured by compensatory mechanisms. Because of this biological complexity, multi-metabolite panels are required instead of single-analyte methods [102,103].

8.3 Technical constraints and analytical considerations

Considerable difficulties still exist in spite of analytical advancements. For routine clinical use, inter-laboratory variability (CV 15-35%) is above tolerable bounds. Metabolite instability necessitates specific collection techniques, which restricts practical implementation, while matrix effects in biological samples provide systematic bias [104,105].

While point-of-care technologies help to overcome some of these restrictions, they also bring with them other difficulties, such as limited analytical range, temperature sensitivity, and calibration drift. Comparing quality assurance programs to traditional clinical chemistry, they are still in their infancy [106,107].

8.4 Barriers to Implementation and Economics

The current expense of analysis ($75-250 per panel) is a major deterrent to routine use. Few studies have examined cost-effectiveness, and the majority of economic estimates are based on theoretical models rather than empirical evidence. Employee training and significant infrastructure investments are necessary for healthcare system integration [108.109]. The regulatory processes for biomarker validation are still costly and intricate, costing between $8 and $20 million per application. Regulatory approval and worldwide implementation are made more difficult by the absence of standardized international standards [110,111].

8.5 Research Restrictions and Upcoming Needs

Population Diversity:

Generalizability to communities around the world is limited because the majority of validation studies come from North American and European populations. Ethnic heterogeneity in metabolite levels caused by genetic variations necessitates population-specific reference intervals [112,113].

Absence of longitudinal data: There are still few long-term outcome studies that relate metabolite alterations to clinical outcomes. Most studies only follow up for three years, which is not long enough to examine the course of chronic diseases. Prognostic biomarker validation is hampered by this constraint [114,115].

Standardization Challenges: Method harmonization is still progressing slowly, despite worldwide efforts. There are still obstacles to clinical adoption due to disparate analytical platforms, sample collecting procedures, and data interpretation methodologies.

9. Recommendations

We advise bringing redox metabolite biomarkers into clinical practice via extensive longitudinal validation, standardized procedures, and combined biomarker panels, based on 115 studies and a meta-analysis of 28,447 individuals. When there are limitations with traditional indicators, clinicians should use them to integrate results with clinical data. Pilot projects, employee training, and cost-effectiveness evaluation should be implemented by healthcare systems, and

regulators should streamline approval processes and standardize requirements. Al-driven interpretation, low-cost point-of-care technology, and academic partnerships for practical validation should be given top priority by industry partners.

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