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Beyond antioxidant activity: Rethinking the biological mechanisms of food-derived bioactive compounds

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Abstract
Traditionally, bioactive compounds from food have been characterized primarily based on their antioxidant activity. However, increasing evidence suggests that their biological effects cannot be fully explained by direct free-radical scavenging alone. Beyond the conventional antioxidant mechanisms, food components such as polyphenols, carotenoids, organosulfur compounds, bioactive peptides, terpenoids and others may interact with cellular signaling networks, transcription factors, metabolic sensors and the gut microbiota, inducing adaptive responses. This review critically revisits the biological mechanisms underpinning the health effects of bioactive compounds derived from food, with a focus on redox signaling, cellular stress adaptation, inflammation, metabolic regulation, mitochondrial function and host-microbiota interactions. An emerging concept is that hormesis may be an important mechanism by which relatively low physiological concentrations of dietary compounds activate endogenous cytoprotective pathways such as Nrf2-mediated cytoprotective responses, rather than simply acting as direct antioxidants. The review also discusses modulation of NF-κB, AMPK, SIRT1, mitochondrial pathways, autophagy, epigenetic processes and gut microbial metabolism. Special attention is given to bioavailability, metabolic transformation and the potential that circulating metabolites or microbiota-derived products rather than parent compounds may be important biological effectors. Determinants of biological activity such as food matrix, processing, dose and inter-individual variability are also considered. Here, we bring together molecular, cellular, microbial and nutritional views to suggest a paradigm shift away from an antioxidant-centric interpretation of food bioactives toward a systems-based understanding of them as biological signaling modulators. Such a framework may enhance interpretation of mechanistic evidence and underpin more rational development of functional foods, nutraceuticals and precision-nutrition strategies.

Keywords: Bioactives in foods, polyphenols, redox signalling, hormesis, gut microbiota, nutraceuticals

Introduction

Bioactive compounds derived from foods have been of great interest to researchers as potential modulators of human health, especially since diets rich in fruits, vegetables, whole grains, legumes, spices and fermented foods have been linked to lower risk of several chronic diseases. Historically, these benefits have often been attributed to the antioxidant properties of dietary polyphenols, carotenoids, peptides, vitamins and other phytochemicals. However, the antioxidant paradigm explains only part of their biological activity. Many compounds are found in foods at concentrations far below those that are needed to scavenge reactive species in any significant way directly. However, their metabolites may have biological effects after extensive transformation and absorption in the gastrointestinal tract.

Recent evidence indicates that bioactives from food may act as signaling molecules and metabolic modulators affecting cellular defense, inflammation, mitochondrial activity, energy metabolism, autophagy and epigenetic regulation and host-microbiota crosstalk. Instead of merely scavenging reactive oxygen species, some compounds might activate the endogenous adaptive responses via pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-κB (NF-κB), AMP-activated protein kinase (AMPK) and sirtuin signaling. Thus, their biological effects may be related to controlled modulation of cellular stress responses rather than direct antioxidant action alone.

This new perspective prompts a reconsideration of how nutraceutical bioactivity is studied and interpreted. Thus, this review addresses biological mechanisms of food-derived bioactives beyond traditional antioxidant activity, such as molecular signaling, metabolism, microbiota interactions, bioavailability and physiological responses, to provide a more comprehensive mechanistic framework for their potential health effects.

Methodology

1. Review design

This review has been developed as a structured narrative review to critically assess the biological mechanisms by which food-derived bioactive compounds can affect human physiology beyond their classical antioxidant activity. The evidence synthesis was organized around the transition from direct chemical antioxidant effects to redox signaling, adaptive stress responses, inflammatory regulation, metabolic signaling, mitochondrial function, epigenetic regulation and gut–microbiota interactions. This broader understanding is reflected in the recent literature, in particular the appreciation that physiological concentrations of many polyphenols may act through signaling and

endogenous defense mechanisms rather than solely through the direct scavenging of radicals.

2. Literature-search period and databases

The selected literature was published from January 2021 to September 2026. Searches were designed to capture recent mechanistic, nutritional and translational evidence from major scientific databases such as Pubmed/MEDLINE, Scopus, Web of Science, ScienceDirect and Google Scholar. The following combinations of keywords and Boolean operators were used:- “bioactive compounds” AND biological mechanisms “food derived”
“Dietary bioactives” AND signaling pathways

- “polyphenols” redox signaling
- “polyphenols” AND Nrf2 AND NF-kB”
- hormesis AND “food bioactives”
- “cellular stress” AND “dietary phytochemicals”
- "bioactive compounds" AND AMPK AND SIRT1
- mitochondrial function AND “food-derived compounds”
- Polyphenols” AND gut microbiota metabolites
- "dietary bioactives" AND epigenetics
- “bioactive peptides” AND mechanism(s)
- "food bioactives" AND bioavailability
- “polyphenols” AND microbial metabolites
- “bioactive compounds” AND “food matrix”
- “nutraceuticals” AND systems biology
- “food bioactives” AND precision nutrition.

We intentionally employed a broad search strategy because the biological effects of food bioactives are broad and span nutritional biochemistry, molecular biology, microbiology, food science and clinical nutrition.

3. Evidence-selection criteria

We focused on peer-reviewed studies and authoritative reviews published between 2021 and 2026 that provide mechanistic evidence for food-derived compounds or their metabolites. Special attention was paid to the literature dealing with:
1. Molecular signaling pathways 2. Redox-sensitive transcription factors 3. Inflammatory signaling 4. Cellular stress and hormesis 5. Mitochondrial regulation 6. Metabolic signaling 7. Autophagy and cellular adaptation 8. Gut microbiota mediated metabolism 9. Bioactive metabolites 10. Bioavailability and biotransformation 11. Human translational evidence
Where conclusions about physiological or health outcomes were discussed, human intervention studies were prioritized. Mechanistic *in vitro*, animal and computational studies were included where they contributed to understanding molecular pathways, but were acknowledged for their limitations for direct human extrapolation.

4. Conceptual framework

The literature was synthesized in a mechanism-first framework rather than a compound-by-compound catalog. The evidence was grouped by biological sequence:
Food source bioactive compound digestion and metabolism circulating/locally produced metabolites molecular target signaling pathway cellular response tissue/systemic response.
This framework is particularly suitable for polyphenols, because gut microbes can transform ingested compounds into metabolites which might show significant differences in biological activity compared to their parental compounds. Recent evidence suggests that the composition of an individual’s microbiome can modulate the production of such metabolites, and thus contribute to inter-individual differences in response. Journal of Nutrition

5. Antioxidant activity versus signalling activity

Direct antioxidant activity and biological redox modulation were clearly analytically differentiated. Therefore, chemical antioxidant assays were not regarded as equivalent to cellular or physiological antioxidant effects. The current literature is increasingly skeptical toward the ability of traditional antioxidant assays in test tubes to predict outcomes in biological systems and instead focuses on redox sensitive signaling and endogenous defense systems. PMC The review therefore considered pathways such as Nrf2/KEAP1, NF-κB, AMPK, SIRT1, MAPK, PI3K/Akt, mitochondrial stress responses and autophagy and the possible role of hormetic signaling. Recent reviews have shown that low-dose exposure to phytochemicals can activate adaptive cellular defense pathways, whereas higher concentrations may lead to differential, or even adverse, biological responses.

6. Gut microbiota and metabolite-mediated mechanisms

Since many food-derived bioactives undergo extensive transformation prior to entering systemic circulation, microbiota-mediated biotransformation was also discussed separately in the review. Special emphasis was given to microbial metabolites, short chain fatty acids, phenolic metabolites and other products formed during gastrointestinal metabolism.
Therefore, it was suggested that the gut microbiota is not only a secondary target but also a potential biological mediator between dietary bioactives and host signaling. There is evidence that microbial conversion can result in metabolites with different biological properties than the parent dietary compounds.

7. Synthesis and interpretation

The selected literature was synthesized into four main mechanistic domains: (i) redox and stress signaling; (ii) inflammation and metabolic regulation; (iii) mitochondrial, epigenetic and cellular adaptation; and (iv) gut–microbiota–host interactions.
In the final synthesis, dose, bioavailability, food matrix, processing, metabolism and inter-individual variability were also considered as these factors can have a significant impact on the delivery of a bioactive compound to a biologically relevant site and in what chemical form.
This approach allows the review to move from the classical question of “Does this compound have antioxidant activity?” to the more biologically relevant question of “How does this food-derived compound or its metabolite interact with biological signaling networks under physiologically relevant conditions?” Recent work increasingly supports this shift to a systems-level interpretation of dietary bioactivity.

From Antioxidant Capacity to Biological Signalling

Bioactive compounds from food have traditionally been tested for their ability to scavenge reactive oxygen species

(ROS) or to reduce oxidative damage in chemical assay systems. However this interpretation is not sufficient any more to explain their biological effects *in vivo*. Many phytochemicals are extensively digested, conjugated and microbial transformed upon ingestion and circulating concentrations may be far below those required for direct chemical scavenging. Their physiological effects may therefore be more influenced by their ability to interact with cellular sensors and signaling networks than by direct antioxidant chemistry alone [1, 3].

There is an important distinction between **antioxidant action** and **redox regulation**. ROS are not only deleterious molecules but at controlled concentrations act as signaling intermediates participating in proliferation, differentiation, metabolism and adaptive stress responses. Excessive ROS removal may thus interfere with normal signaling. Instead, foods could deliver bioactives that operate on redox-sensitive proteins and transcription factors and modulate endogenous defense systems [4, 5].

This is especially true for polyphenols as their metabolites can interact with cellular signaling pathways at concentrations that are physiologically relevant. Some compounds may activate endogenous cytoprotective mechanisms involving Nrf2, AMPK, SIRT1 and related pathways, rather than simply acting as radical scavengers [2, 6]. Activating these systems can upregulate expression or activity of endogenous antioxidant and detoxification enzymes like superoxide dismutase, catalase, glutathione-related enzymes and NAD(P)H:quinone oxidoreductase 1.

The biological response may also depend on **dose, duration of exposure and the context of the cell**. At low to moderate levels of exposure, some phytochemicals can induce controlled adaptive stress signaling, and thus stimulate cellular defense, but higher concentrations may result in pro-oxidant activity or cellular toxicity [5, 7]. This concentration-dependent behavior provides a mechanistic basis for the concept of **hormesis**, where a mild biological challenge triggers protective adaptation.

Therefore, the biological relevance of food bioactives should not be evaluated merely according to their behavior in chemical antioxidant assays. A more meaningful framework is their ability to regulate **redox-sensitive signaling, transcriptional responses, inflammation, mitochondrial function and metabolic adaptation** This switch provides an explanation for the observation that compounds with modest direct antioxidant capacity may have substantial biological effects in cellular and physiological systems.

Molecular Mechanisms beyond Direct Antioxidant Effects

1. Nrf2/KEAP1 Signalling and Endogenous Cytoprotection

One of the most important mechanisms by which food-derived bioactives may influence cellular defense is modulation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (KEAP1) pathway. In basal condition, KEAP1 promotes Nrf2 degradation, thereby keeping the transcriptional activity at a relatively low level. Alterations in the cellular redox environment can activate the escape of Nrf2 from degradation, translocation to the nucleus and regulation of genes via the antioxidant response element that are important for the protection of the cell [8, 9].

Polyphenols and other dietary constituents may influence this pathway by interacting with redox-sensitive regulatory proteins or by causing mild adaptive stresses. Their biological activity may therefore be related to the activation of the endogenous antioxidant and detoxification systems rather than a direct scavenging of ROS [8]. Upregulation of enzymes associated with glutathione synthesis, xenobiotic metabolism and cellular antioxidant defense may improve the capacity of cells to respond to subsequent oxidative challenges.

This mechanism also demonstrates why chemical assays cannot be relied upon to predict the antioxidant activity of a food bioactive. A compound may exhibit a quite modest radical-scavenging capacity but induce major cellular effects via transcriptional regulation. However, the physiological relevance of Nrf2 activation is contingent on the concentration, the length of exposure and the cellular context.

2. NF-κB and Inflammatory Signalling

Chronic low-grade inflammation is a key biological link between diet and metabolic disorders. Bioactives derived from food have been investigated for their capacity to modulate inflammatory signaling, especially the nuclear factor-κB (NF-κB) pathway [10, 11].

NF-κB controls the transcription of a large number of inflammatory mediators. Excessive or prolonged activation can increase expression of cytokines, chemokines and enzymes of inflammation. Several polyphenols and other food-derived compounds have been shown to affect upstream kinases and regulatory proteins involved in the activation of NF-κB.

Crucially, this effect should not be seen as just an extension of antioxidant activity. Redox status and inflammatory signaling are interlinked, but bioactives can affect inflammatory pathways through multiple mechanisms including kinase regulation, transcriptional control and modulation of cellular stress responses [10].

This offers a mechanistic explanation for the observation that dietary patterns rich in polyphenol-containing foods can influence inflammatory processes even when circulating concentrations of the parent compounds are relatively low.

3. AMPK, SIRT1 and Metabolic Regulation

Bioactives from food may also affect cellular energy sensing pathways. AMP-activated protein kinase (AMPK) is a critical metabolic sensor responding to the cellular energy status and sirtuin 1 (SIRT1) is involved in metabolic regulation, mitochondrial adaptation and transcriptional control [12, 13].

Activation of these pathways can affect glucose utilization, fatty acid oxidation, mitochondrial biogenesis and cellular energy homeostasis. Accordingly, several dietary polyphenols have been studied as potential modulators of metabolic signaling rather than antioxidants.

The relationship of dietary bioactives with these pathways is complicated by the fact that experimental concentrations tend to be higher than can be attained by normal food intake. Moreover, some compounds may act indirectly through metabolites or gut microbial products rather than the parent molecule [14].

Thus mechanistic statements should differentiate between direct molecular interaction, downstream pathway modulation and physiological effects observed after dietary exposure.

4. Mitochondrial Function and Cellular Energy Homeostasis

Mitochondria are not only major sources but also important targets of cellular oxidative stress. Mitochondrial overproduction of ROS can result in impaired energy metabolism, altered membrane potential and activation of stress-related pathways. Conversely, mild mitochondrial stress may also elicit adaptive responses that increase cellular resilience.

The effects of food-derived bioactives on mitochondrial biogenesis, respiratory function, membrane integrity, mitophagy and antioxidant defense have been studied [15, 16]. Polyphenol metabolites may modulate AMPK–SIRT1–PGC-1α related signaling, thereby affecting mitochondrial adaptation.

This relationship further emphasizes the limitations of considering dietary bioactives as ROS scavengers only. Instead of just neutralizing ROS after they have formed, a compound that modifies mitochondrial signaling may influence the source, production and handling of ROS.

5. Autophagy and Cellular Quality Control

Another important cell mechanism that could be affected by food-derived bioactives is autophagy. Autophagy contributes to cellular quality control and adaptation to metabolic stress by controlled degradation and recycling of damaged proteins and organelles [17].

Several phytochemicals have been studied for their ability to affect autophagic pathways through AMPK, mTOR and related signaling networks. The regulation of autophagy might be particularly important for mitochondrial quality control since the removal of dysfunctional mitochondria might reduce excessive ROS production.

Autophagy, however, is highly context-dependent. Excessive activation or suppression might result in different biological consequences depending on cell type, metabolic state and disease context. Thus, any claims of autophagic modulation by nutraceuticals should be taken with caution.

6. Epigenetic Regulation

Epigenetic regulation such as DNA methylation, histone modification and non-coding RNA expression is an emerging dimension of food-bioactive research [18]. Some dietary compounds or their metabolites have the capacity to influence the enzymes affecting epigenetic modifications and consequently modulate gene expression without affecting the DNA sequence.

Metabolites of polyphenols are of particular interest since they are able to reach tissues after absorption or microbial transformation. Habitual dietary exposure may be linked to longer-term alterations in the cellular phenotype through epigenetic mechanisms.

But much of the evidence available is mechanistic or pre-clinical. Additional research is required to determine the physiological concentrations that induce specific epigenetic effects and the duration of such effects in humans.

7. The Importance of Hormesis

The concept of hormesis offers a useful framework for integrating many of these mechanisms. Rather than eliminating all reactive molecules, some food-derived compounds may generate a relatively mild cellular stimulus that activates endogenous protective responses [7, 19].

This may result in a biphasic relationship where low or moderate exposure induces adaptation, but excessive exposure may become ineffective or harmful. Such behavior may explain why biological activity does not always increase in proportion to the dose.

This distinction is important for nutraceutical research. Higher doses of a purified bioactive do not necessarily result in greater physiological benefit. Dose–response relationships need to be understood within the framework of food matrices, metabolism, tissue distribution and cellular adaptation.

Food-Derived Bioactives as Multitarget Biological Modulators

1. Polyphenols and Cellular Signalling

Polyphenols are one of the most studied groups of bioactives from food. Flavonoids, phenolic acids, stilbenes, lignans and other subclasses present a great structural diversity which is the basis of their biological diversity. Many are initially described in terms of antioxidant properties, but their biological effects include modulation of transcription factors, kinases, enzymes, membrane-associated processes and microbial metabolism [20, 21].

One major challenge is that plasma concentrations of many parent polyphenols are considerably lower than the concentrations often used in *in vitro* experiments. Conjugation reactions and microbial transformation can lead to the formation of glucuronides, sulfates and minor phenolic metabolites with different biological properties after administration [14, 20].

Thus, to understand their true biological mechanisms, it is important to understand the metabolic fate of polyphenols. The biological agent of interest may not necessarily be the same compound as was originally present in the food.

Table 1: Major Food-Derived Bioactive Compounds and Their Biological Mechanisms beyond Direct Antioxidant Activity

Bioactive class	Representative food sources	Major biological targets/pathways	Potential biological effects
Polyphenols	Berries, tea, cocoa, grapes, onions, spices	Nrf2/KEAP1, NF-κB, AMPK, SIRT1, MAPK	Cellular defence, inflammatory regulation, metabolic adaptation
Flavonoids	Citrus, berries, tea, apples, legumes	Nrf2, NF-κB, PI3K/Akt, MAPK	Redox signalling, vascular regulation, inflammatory modulation
Phenolic acids	Whole grains, coffee, fruits, vegetables	Nrf2, AMPK, inflammatory signalling	Metabolic regulation and cellular stress adaptation
Carotenoids	Carrot, tomato, leafy vegetables, pumpkin	Nrf2, mitochondrial and inflammatory pathways	Cellular protection and modulation of oxidative-stress responses
Organosulfur compounds	Garlic, onion, cruciferous vegetables	Nrf2, NF-κB, detoxification enzymes	Cytoprotective and inflammatory regulation
Bioactive peptides	Milk, eggs, legumes, cereals, fish	ACE, opioid receptors, AMPK and cellular signalling	Cardiometabolic, immunomodulatory and regulatory effects
Dietary fibres	Whole grains, legumes, fruits,	Gut microbiota, SCFA receptors,	Barrier support, metabolic regulation

	vegetables	intestinal signalling	and immune modulation
Fermentation-derived metabolites	Yogurt, fermented cereals, vegetables, legumes	Microbiota–host signalling, SCFA pathways	Gut barrier, immune and metabolic effects
Microbial phenolic metabolites	Generated from polyphenol-rich foods	Host receptors, cellular signalling, epigenetic pathways	Potential systemic and tissue-specific biological effects

Footnote: The biological effects listed represent mechanistic outcomes reported across experimental and nutritional studies and should not be interpreted as evidence of equivalent clinical efficacy. The actual response depends on dose, bioavailability, metabolism, food matrix, microbial transformation and individual physiological characteristics.

2. Bioactive Peptides and Receptor-Mediated Mechanisms

Food proteins are capable of releasing biologically active peptides during digestion, fermentation or enzymatic hydrolysis. These peptides may interact with enzymes, receptors or signaling pathways and their potential antihypertensive, antioxidant, anti-inflammatory and metabolic effects have been studied [22].

Peptides have the potential to act through relatively specific interactions with biological targets, unlike small molecule polyphenols. Their activity is a function of amino-acid sequence, peptide size, structural characteristics, digestive stability and absorption.

Thus, the identification of bioactive peptides requires an integration of proteomics, gastrointestinal digestion, peptide sequencing and functional validation instead of a simple chemical antioxidant assay.

3. Dietary Fibre, Microbiota and Microbial Metabolites

Another example of why direct measurements of antioxidants cannot be used to understand the biological effects of food components is the case of dietary fiber. Fermentable fibers may be fermented by intestinal micro-organisms to yield metabolites, such as short-chain fatty acids, that affect host physiology [23].

Acetate, propionate and butyrate can participate in energy metabolism, epithelial maintenance, immune regulation and signaling through G-protein-coupled receptors and other molecular mechanisms. Fiber is therefore not simply an inert element of nutrition, but a substrate for microbiota-mediated biological communication.

This concept further broadens the definition of a bioactive compound. In some cases, physiological important molecule can be formed by microbial metabolism after food ingestion.

4. Fermentation-Derived Bioactives

The fermentation process can alter the chemical composition of foods and produce metabolites that are not present in abundance in the original ingredients. [24] Microbic enzymes can hydrolyze proteins, transform polyphenols and produce organic acids, peptides and other metabolites.

Thus, fermented foods may provide a complex mixture of parent compounds and fermentation products. The biological activity of the final food may be quite different from that of the substrate before fermentation.

This is important for the development of nutraceuticals, as processing can be deliberately designed to enhance the production or bioavailability of desirable metabolites.

5. Gut–Brain and Gut–Immune Interactions

The gut microbiota is a key interface between dietary bioactives and systemic physiology. Microbial metabolites may interact with intestinal epithelial cells, immune cells and neural signaling systems, suggesting possible pathways to link food intake with immune and neurological processes [23, 25].

Polyphenols and dietary fibers might change the microbial community composition as they move through the gut. This establishes a bidirectional relationship in which dietary compounds affect the microbiota and the microbiota dictates which metabolites are biologically available.

These mechanisms are of particular relevance to emerging concepts surrounding gut–brain axis, neuroinflammation and metabolic regulation. But causal relationships in humans remain harder to establish than associations in observational or preclinical research.

6. Bioavailability and Biotransformation

Biological efficacy is highly dependent on bioavailability. A food may contain a high concentration of a bioactive compound, but only a small fraction may be available in systemic circulation in an active form.

Exposure is influenced by absorption, metabolism in the intestinal wall and liver, plasma protein binding, tissue distribution and elimination. For polyphenols, microbial metabolism can further diversify the compounds reaching circulation [14].

Thus the traditional approach to ranking foods according to total content of a certain phytochemical may provide an incomplete picture of biological potential. Future nutraceutical research should focus increasingly on bioaccessible, metabolized and physiologically achievable forms.

7. Food-Matrix Effects

Bioactive compounds in foods are rarely found alone. Absorption and activity of proteins, lipids, fiber, minerals and other matrix components can be modulated by them. Food processing may also change molecular composition, solubility and release.

For example, thermal processing can destroy some compounds but increase the bioaccessibility of other compounds. Fermentation can convert poorly available compounds into more easily absorbable metabolites.

Thus, biological activity should be increasingly studied at the food or formulation level, rather than assuming that activity of purified compound will be replicated after consumption of the full food.

8. From Single Targets to Network Pharmacology

Chronic diseases do not have a single molecular target but interconnected pathways. Thus food-derived bioactives may act through multiple pathways with modest effects rather than a strong effect at one particular target.

Network pharmacology and systems biology approaches offer the possibility to map the interactions between bioactive compounds, metabolites, molecular targets and physiological pathways [26]. This approach is particularly appropriate for foods, as dietary exposure concerns complex

mixtures of compounds, not simple pharmaceutical-like molecules.

The emerging view is thus one of network modulation, not single target action, and biological effects are the consequence of the cumulative interaction of multiple molecular and microbial pathways.

Translational Relevance, Limitations and Emerging Opportunities

1. From *In vitro* Antioxidant Assays to Physiological Relevance

One of the biggest challenges in food-bioactive research is the frequent extrapolation of results obtained from chemical antioxidant assays to human health effects. Assays such as DPPH, ABTS, FRAP and ORAC can provide useful information about chemical reactivity but they do not replicate the complexity of digestion, metabolism, cellular uptake, tissue distribution or physiological signaling. Thus, a compound with potent radical-scavenging activity *in vitro* might have weak direct antioxidant activity after consumption.

Therefore, physiologically relevant concentrations should be a key consideration in the evaluation of bioactive compounds. Studies at concentrations far higher than can be achieved by dietary exposure may elucidate molecular mechanisms but should not be taken to indicate that similar effects will occur in humans [27]. Hence, the difference between chemical antioxidant capacity and biological antioxidant response is of importance for nutraceutical research.

2. Dose–Response Relationships and Hormesis

Food-derived compounds can have nonlinear dose–response relationships for their biological effects. Low concentrations may activate adaptive cellular pathways, whereas higher concentrations may induce different responses due to altered signaling, metabolic saturation or pro-oxidant effects [19, 28].

Hormesis can explain this phenomenon. A mild biological insult may trigger endogenous defense mechanisms, resulting in a state of enhanced cellular resilience. This concept defies the assumption that higher concentrations of a bioactive will necessarily translate into proportionally higher health benefits.

In the development of nutraceuticals, this means that optimal biological exposure may be more important than maximal exposure. Future intervention studies should therefore examine multiple physiologically relevant doses and consider exposure duration rather than focusing on high-dose supplementation alone.

3. Influence of Food Matrix and Processing

The food matrix in which a bioactive compound is present has a significant impact on the biological activity of the compound. Proteins, lipids, carbohydrates and fiber can modify solubility, digestion, intestinal release and absorption. Processing may also change chemical structure and accessibility [29].

Fermentation is a key example, where the metabolism of microbes can convert precursor compounds into novel metabolites with different biological activities. Similarly, bioaccessibility may be decreased or increased by thermal processing depending on the compound and food matrix.

This means that the health potential of a food cannot be predicted by measuring the concentration of individual bioactives before processing. Measures of bioaccessibility and biological availability following food preparation may be more meaningful.

4. Inter-Individual Variability and Personalised Nutrition

Individual responses to the same dietary bioactive may differ due to differences in genetics, age, metabolic status, medication use, diet, intestinal microbiota and lifestyle. The gut microbial composition is particularly important as microorganisms can influence the degree to which dietary compounds are converted into biologically active metabolites [14, 25].

This variability is an opportunity for customized nutrition. Future approaches might integrate microbiome, metabolomic and clinical information to identify individuals that are more likely to respond to specific dietary interventions rather than assuming a given bioactive will have identical effects across populations.

Such approaches could move the development of nutraceuticals from a one compound fits all model to a more personalized strategy based on biological phenotype and metabolic capacity.

5. Multi-Omics and Systems Biology

The growing complexity of food-derived bioactive mechanisms calls for approaches capable to investigate several biological levels simultaneously. Transcriptomics allows to detect changes in gene expression, proteomics to detect altered proteins and signaling networks, metabolomics to detect circulating or microbial metabolites and microbiome sequencing to detect changes in microbial communities [26, 30].

These datasets may be integrated to help establish relationships between food intake, bioactive metabolism, molecular signaling and physiological outcomes.

For instance, dietary intervention can be evaluated by measuring simultaneously changes in microbial composition, microbial metabolites, inflammatory biomarkers, gene-expression signatures and metabolic parameters. These approaches may provide a more robust mechanistic evidence than measuring a single antioxidant marker.

6. Artificial Intelligence and Predictive Bioactive Discovery

Tools are emerging that use artificial intelligence and machine-learning to identify relationships between chemical structures, food composition, biological targets and health outcomes. Computational approaches can help screen large numbers of compounds and predict molecular interactions before they are tested experimentally.

For food-derived bioactives, AI could potentially exploit food composition databases, metabolomics, molecular docking, microbiome profiles and clinical data to identify candidate compounds or combinations with promising biological activity.

However, computational prediction should be viewed as a tool to generate hypotheses, not as a replacement for experimental and clinical validation. The complexity of food matrices and human metabolism means that predicted molecular interactions do not necessarily translate into measurable physiological effects.

7. Combination Effects and Food-Based Synergy

Foods contain mixtures of bioactive compounds that may interact in an additive, synergistic or antagonistic fashion. Therefore, a fruit, spice, wholegrain or fermented food may have biological effects that are not explained by a single compound.

This distinction is essential between food-based bioactivity and nutraceutical supplementation. Isolated compounds are amenable to clear experimental analysis but may fail to mimic the complex interactions occurring in the natural food matrix.

Future research should thus investigate combinations of polyphenols, fibers, peptides, microbial metabolites and micronutrients using physiologically relevant food models. Network-based approaches may be particularly helpful to identify complementary mechanisms.

8. Translating Mechanisms into Functional Foods and Nutraceuticals

Functional foods that target specific biological functions can be developed by gaining mechanistic insights into food bioactives. However, translation requires several steps: identification of a plausible mechanism, validation at physiologically relevant concentrations, assessment of bioavailability, validation in appropriate models and finally demonstration of meaningful outcomes in human studies.

A mechanistically attractive compound should, therefore, not be indiscriminately classified as an effective nutraceutical. Evidence should go from chemical activity to cellular mechanism to bioavailability to human biomarkers to clinically meaningful outcomes.

This hierarchy can help to minimize overinterpretation and to increase the scientific credibility of functional-food and nutraceutical claims.

9. Future Directions

Future work needs to break away from the traditional practice of reporting antioxidant capacity as the main indicator of food-bioactive efficacy. More emphasis should be placed on physiologically achievable concentrations, metabolite mediated effects, redox signaling, gut microbial transformation and adaptive cellular responses.

The next generation of studies should include controlled human interventions and metabolomics, microbiome analysis, proteomics and transcriptomics in an effort to identify biological responders and non-responders. This may help to elucidate whether parent compounds, host metabolites, microbial metabolites, or combinations of these components, cause specific health effects.

Another important direction is mechanism-guided food design. Functional foods could be designed against a specific biological target, for example to support Nrf2-mediated cytoprotection, metabolic signaling, intestinal barrier function or microbiota-derived metabolite production, instead of adding a bioactive compound because of its high antioxidant capacity.

AI-assisted modeling could further assist this process, by linking food composition with molecular targets, metabolic pathways and individual response characteristics.

The field should finally move from ‘How antioxidant is this food?’ to ‘What biological pathways does this food impact, at what physiological exposure, by which metabolites and in whom?’ This change may provide a more rigorous mechanistic basis for future research in nutraceutical, functional-food and precision-nutrition research.

Limitations

Although the evidence of bioactive compounds from food is increasing, several limitations still exist in comprehending their biological mechanisms. First, most of the mechanistic evidence is based on *in vitro* experiments at concentrations that may not be physiologically achievable following normal dietary consumption. Thus, molecular effects observed experimentally cannot be directly translated into human health effects. Secondly, there is extensive metabolism by intestinal, hepatic and microbial systems so that the compound tested experimentally may be quite different from the chemical species that actually reaches tissues. Third, differences in food matrix, processing, digestion, absorption and individual microbiota composition may lead to a large variation in bioactive exposure and response. Fourth, numerous studies are focusing on isolated compounds, whereas foods are complex mixtures that may act synergistically or antagonistically. Finally antioxidant assays are still frequently used although they are limited in their ability to predict biological activity *in vivo* . These factors underscore the importance of physiologically relevant experimental models, extensive metabolite profiling, standardized methodologies and well-designed human intervention studies to establish causal relationships between dietary bioactives, molecular signaling and clinically meaningful outcomes.

Conclusion

The biological significance of bioactive compounds from food goes far beyond their conventional antioxidant classification. Their potential effects are due to complex interactions with cellular signaling networks, metabolic pathways, mitochondrial processes, epigenetic mechanisms and the gut microbiota. This broader view allows a more realistic understanding of how foods and their constituent compounds can impact physiological processes.

Emerging evidence suggests that direct neutralization of reactive species is only one facet of dietary bioactivity. Food-derived compounds may rather exert their action as biological signals to stimulate endogenous protective responses, regulate inflammation, influence energy metabolism and modify cellular adaptation. Their metabolites and transformation products from microbiota might also contribute importantly to these effects.

This mechanistic view has important implications for the development of nutraceuticals and functional foods. Future products should not be designed on the basis of high antioxidant scores, but should consider bioavailability, physiological exposure, molecular targets, food-matrix interactions and individual biological variability. An awareness of these elements can allow a distinction between compounds with real translational potential and those with apparent activity limited to experimental models.

A systems-level approach combining food chemistry, molecular biology, microbiology, metabolomics and nutrition science may offer the most effective framework for understanding dietary bioactivity. Such integration could allow for the development of foods targeting specific biological functions, rather than broad claims of antioxidant protection.

Redox biology remains critically important, but it is increasingly recognized that the study of food-derived bioactives goes far beyond antioxidant activity and that antioxidant responses are but one element of a broad network of cellular communication and adaptation. Such a conceptual shift can help to promote mechanistic research and underpin more scientific approaches to functional foods, nutraceuticals and personalized nutrition.

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Authors' contributions
NM conceived the review, developed the methodology, conducted the literature search and evidence synthesis, prepared the tables and figures, and wrote the original draft. JW supervised and validated the work and critically reviewed, revised and edited the manuscript. Both authors read and approved the final manuscript and agreed to be accountable for the integrity of the work.

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