ECRONICON OPEN ACCESS

EC NUTRITION
Review Article

Universal Evolutionary Capacitor Switch Operation Regulation Gimmicks Driving Illness and Natural Cure: Food and Environment are the Key Modulating Drivers

Faiza Abdur Rab*

Assistant Professor, Department of Food Science and Technology, University of Karachi, Karachi, Pakistan

***Corresponding Author:** Faiza Abdur Rab, Assistant Professor, Department of Food Science and Technology, University of Karachi, Karachi, Pakistan.

Received: December 17, 2025; **Published:** February 05, 2026

Abstract

The genomic homology between *Saccharomyces cerevisiae* and the human genome forms the basis for studies elucidating biological processes in living systems at the molecular level. Research indicates that the *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) and *CTR1* gene that encodes for membrane copper transporter 1 protein (ctr1p) are part of same gene regulatory network and are reciprocally regulated in response to copper concentration gradient levels dependent manner modulated by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts through feedback mechanism at the transcriptional level. It demonstrates that physical, chemical and biochemical stimuli or biological injury can alter the effects of mutations that impair the function of essential genes operating within the same regulatory network. This process can enhance the activity of weaker genes. When biochemical reaction cascades function under stress conditions, their framework is altered. Rab (2007) revealed that, under stress conditions, the regulation and operation of genes network pathways and ongoing biochemical reactions modify their functional biochemical and chemical potentials, targets and consequences. For example, under stress condition in del *CTR1* gene (that encodes for membrane copper transporter1protein (ctr1p)) yeast cells, when copper ions are sufficiently supplied to Cu-Zn superoxide dismutase (sod1p) by the *Lys 7/CCS* gene product (*Lys 7/CCS* gene is down-regulated or is turned off under non-functional or in absence of *CTR1* gene that encodes for membrane copper transporter 1 protein (ctr1p)) the cell populations regain their viability proportion same as the wild type yeast cell populations exhibit on exposure with same strength of stressor. This restoration of activity of *SOD1* gene (that encodes for Cu-Zn superoxide dismutase (sod1p)) s product, a protein that binds copper and zinc ions in its molecular structure to destroy free superoxide radicals including those generated by electron transport chain (respiratory chain) in absence of *CTR1* gene, which encodes for membrane copper transporter 1 protein (ctr1p), a cell membrane protein that is a high affinity membrane copper transporter; such as Cu-Zn superoxide dismutase (sod1p) molecules acquiring their multifaceted chemical and biochemical potentials involving stereochemistry and enzymatic activity and their shifts while enabling the knock out yeast cell populations to regain survival strength against the stressor in a manner similar to that observed in wild-type yeast strains' populations. These findings question the credibility of traditional understanding related to the mutual relationship that exists among protein dysfunction, cell survival and disease. It also underscores the complexity of genomic operations and biochemical processes which may be governed by genetically and/or epigenetically pre-programmed biochemical cascades alone or are modulated in combination with environmental and dietary drivers. These drivers act upon universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch's regulatory circuit effecting modulators' roles which drive evolution of healthy or unhealthy poorly adopted or well adopted cellular phenotypes influencing the trajectory of disease and recovery.

Keywords: *Gene Operation Regulatory Network; Apoptosis; Epigenetics; Evolution; Food Preparations; Contagious Disease; Non Contagious Illnesses; Natural Health; Food Therapy; Obsolete Knowledge; Academia and Industry Linkage*

Introduction

Web of interactions and emerging challenges

In ancient times, the primary challenges faced by the human populations across different regions of the world were centered on the search for food, defense of lives, for survival, the building of shelters and for management of infectious diseases. These fundamental concerns were essential for ensuring the survival of human societies. However, with the advancement of scientific knowledge, its subsequent application and translation into technology, human habits, social structures and professions have undergone transformation. The interconnection among people shaped by the flow of goods, services and revenue both physically and virtually has given rise to new challenges while simultaneously altering the pre-existing ones. This transformation has permeated nearly every aspect of life.

In biological sciences, the fundamental concept of life is based upon the fact that with an exception of a few RNA viruses, all organisms store their genetic information in Deoxyribonucleic Acid (DNA). This Deoxyribonucleic Acid (DNA) molecule may exist in continuous or non-continuous segments which carry genes that are sequences of nitrogen bases, triplet of them encodes for specific amino acid except for initiation and termination codons. These amino acids are linked together to form polypeptides, the building blocks of protein molecules. The genome, composed of Deoxyribonucleic Acid (DNA) segment or segments, other than viruses, serves as the basic governing unit for structural and functional characteristic features of life. It is responsible for maintaining and regulating genes interactions in naturally pre-programmed manner or altered-programmed manner such as under stress or under certain diseases conditions governing cells structures, functions and fates. The genome also dictates evolutionary pathways that are regulated both by genetically and/or epigenetically driven manners such as by involving either of them or both of them. Metabolic pathways are dynamically regulated in dependent or independent manners and can be modified in response to environmental changes, whether through physical, chemical or biochemical stimuli, in response of an injury or as an outcome of altering oxidative flux alone [1-20].

Genetic information encoded in Deoxyribonucleic Acid (DNA) molecule segment or segments, is passed on to offspring cells which possess the capability to function both individually in a given environment and collectively in form of tissues. These tissues are organized to form organs that function in coordination, constituting the systemic physiology of multicellular biological entities. This genetic information is also transmitted to the offspring of these multicellular organisms through genetically regulated reproductive cycles. Over time, this process accommodates cumulative effects of mutations and epigenetically driven changes, which are influenced by both intracellular and extracellular environmental factors and the food consumed. These effects may be modulated by cellular events or may be independent of them [10-22].

Many studies in fields of biological sciences, medical sciences, food sciences etc. and in the allied domains of knowledge have focused on use of biotechnology and bioinformatics as the findings of Schlessinger., *et al*. (2011) have been widely applied across these domains, contributing to the development of a comprehensive framework. These findings highlight the existence of mutual relationship among protein dysfunction, cell survival and illnesses [23].

Through the application of bioinformatics, particularly in combination with biotechnology as a supporting tool, Deoxyribonucleic Acid (DNA) has been used to drive the creation of Deoxyribonucleic Acid (DNA) encoded chemical libraries aimed at addressing challenges in targeted drug design. These libraries focus on addressing serious challenges that are often difficult to overcome, particularly those related to drug delivery, metabolism, and genes regulatory networks. These challenges are particularly relevant to cellular and systemic physiology as well as their interplay is demonstrated in modulating regenerative potential. They are also linked to cell cycle, and to other cellular events, including adaptation, apoptosis, ferroptosis and necrosis etc. [16-20,24-26].

Generally, the brain's biodynamic physiology, and its pathological pathways, circuits regulatory mechanisms and functional networks operate differently from those of other tissues in the living organisms. As such, diseases of the brain and associated prevention and treatment strategies require distinct approaches to achieve complete cure. Findings derived from studies conducted on isolated living cells, cell lines or genetically altered biological specimens do not always accurately reflect the molecular mechanisms underlying the biological processes, occurring within biological entities in their natural context. The mechanisms may differ when cells operate in isolation, within colonies or as a part of a multicellular systems. Consequently, utilizing bioinformatics and biotechnology, despite their premise, may sometimes yield unreliable results in biological investigations, carrying a high risk of uncovering unpredictable biological threads, such as emergence of COVID19 virus [27-31]. My work which is currently under consideration by reputable scientific journals, presents a comprehensive analysis of how COVID19 virus modulates bodily functions by altering the regulatory operations of genes. This alteration affects biological events at multiple levels across cells, tissues, and physiological systems, determining their fate both at the individual cell level and through cumulative effects determining the fate of infected individuals. The COVID19 virus employs oxidative stress fluxes shifts as a common virulence strategy, which shares triggering stimuli that mimics with those involved in driving pathological pathways associated with neurodegenerative diseases. Furthermore, my work provides evidence that natural food preparations can treat various illnesses, including COVID19 virus driven illnesses manifestations leading to complete recovery. This research introduces the concept of operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch connecting the networks of life across the biological linkage evolutionary tree, influencing key processes such as cells differentiation, growth, repairing process underlying mechanisms, and aging as well as pre-death cellular events leading to apoptosis, ferroptosis, necrosis etc. [2,4-22,27-41].

Additionally, studies conducted on multi-cellular specimens or organisms are often too complex to fully elucidate the underlying molecular mechanisms, particularly because various factors and types of stimuli are involved individually or cumulatively in modulating these mechanisms underlying the ongoing biological events [42].

Universal-evolutionary-capacitor integrated biological evolution linkage tree-regeneration, natural health and natural cure potentials

As discussed earlier, natural food preparations, building the concept of food therapy, reported in the author's work has appeared to be a common player treating a wide range of illnesses both contagious and non-contagious illnesses including COVID19 virus driven manifestations. This work presents the first evidence of a universal evolutionary capacitor, operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch connecting the web of life across the biological linkage evolutionary tree influencing individual cells' differentiation, growth cycle and other cellular events. These processes are regulated at genes networks' operation level involved in playing a key role in cell differentiation, adaption, cell growth and in aging etc. This underlying regulatory framework mechanism also drives aging, repair processes and adaption diversely or drive the cells to opt to pre-death cellular events leading to apoptosis, ferroptosis or necrosis etc. These cellular events are fundamental to maintaining natural health, influencing emergence and onset of diseases and their recovery and the consequences that may lead to complications, with or without mortality. This work offers the first practical demonstration of the presence of a universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn

superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch which functions across biological evolution linkage tree, governing the regeneration potential within species. This universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such-*SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch which is regulated through genomic, epigenomic and non-genomic underlying regulatory mechanisms that adapts to environmental changes and are partly effected by the food consumed. It drives the biological systems to confer altered multifaceted roles of chemical and biochemical species and biologically functional cell organelles particularly under stress conditions, influencing the natural health. This discovery reveals a novel strategy for treating many contagious and non-contagious illnesses leading to complete recovery.

In 2007, a study involving *Saccharomyces cerevisiae,* a yeast with considerable homology to human genome and is a widely used model for studying genes functions, revealed that physical, chemical and biochemical stimuli or an injury can alter the effects of mutations that impair the functions of essential genes operating within the same regulatory network. These phenomena can enhance the activity of weaker genes. Specifically, the study revealed that *SOD1* gene, (that encodes for Cu-Zn superoxide dismutase (sod1p)), a protein that binds copper and zinc ions in its molecular structure, destroys free superoxide radicals including those generated by electron transport chain (respiratory chain) and *CTR1* gene, which encodes for membrane copper transporter 1 protein (ctr1p), a cell membrane protein that is a high affinity membrane copper transporter, are linked through the same genes operations regulatory pathway. These genes are reciprocally regulated at transcriptional level in response to copper concentration gradients modulated by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts through feedback mechanism. The study further indicated that, under stress conditions such as under oxidative stress, both the physiology of the cellular components and the biochemical processes are modulated diversely, ultimately altering the cells' fate. These changes drive the cells, to acquire environmentally well adopted cellular phenotypes in epigenetically and/or genetically pre-programmed manners, thereby limiting the effects of mutations. This adoptive process is one of the underlying processes that drives the cell to escape apoptosis and cellular other death events, in parallel influences cell growth, repairing, aging and other cellular processes. In addition, it creates additional provisions to evade pre-death cellular events leading to apoptosis or other forms of genetically and/or epigenetically regulated cellular death, facilitating the evolution of cell phenotypes better suited to the environment through diversely regulated pre-programmed genes operation framework underlying mechanisms.

Rab (2007) argued that, under stress conditions the balance shifts between holo-Cu-Zn superoxide dismutase (holo-sod1p) such as (Cu(2+)loaded Cu-Zn superoxide dismutase (sod1p) molecular form possessing enzyme activity) molecules and apo-Cu-Zn superoxide dismutase (apo-sod1p) such as (Cu(2+)deficient Cu-Zn superoxide dismutase (sod1p) molecular form lacking enzyme activity) molecules cumulatively drives the cell to opt to evolve into environmentally well adopted cell phenotype without initiating apoptosis process for which the cell needs Cu-Zn superoxide-dismutase (sod1p) in holo-Cu-Zn superoxide dismutase (holo-sod1p) molecular form such as (Cu(2+) loaded Cu-Zn superoxide dismutase (sod1p) molecular form possessing enzyme activity) molecules in contrary to apo-Cu-Zn superoxide dismutase (apo-sod1p) molecular form such as (Cu(2+) deficient Cu-Zn superoxide dismutase (sod1p) molecular form lacking enzyme activity) molecules that is required to evade pre-evolution events. This finding indicates that the general principles of chemistry cannot be directly applied to ongoing biochemical reactions occurring within living systems without necessary modifications particularly under non-physiological conditions such as under stress conditions or under certain disease conditions like cancer. When biochemical reactions' cascades function under stress conditions, their framework is altered. Rab (2007) revealed that, under stress conditions, the regulation and operational framework of genes network pathways and ongoing biochemical reactions modify their functional, biochemical and chemical potentials, targets and consequences. For example, under stress condition in del *CTR1* gene (that encodes for

membrane copper transporter 1 protein (ctr1p)) yeast cells, when copper ions are sufficiently supplied to Cu-Zn superoxide dismutase (sod1p) by the *Lys 7/CCS* gene's product (*Lys7/CCS* gene is down-regulated or is turned off in absence of *CTR1* gene that encodes for membrane copper under non-functional or in transporter 1 protein (ctr1p)) the cell populations regain their viability proportion same as that of the wild type cell populations exhibit on exposure with same strength of stressor. This restoration of Cu-Zn superoxide dismutase (sod1p) molecules' multifaceted chemical and biochemical potentials involving their stereochemistry and enzymatic activity and their shifts enable the knock out yeast cells to regain their survival strength against the oxidative stress in a manner similar to that is observed in wild-type yeast strains in genetically and/or epigenetically driven manners [12-18,33-35,37-69].

SOD1 gene that encodes for Cu Zn superoxide dismutase (sod1p) and *CTR1* gene that encodes for membrane copper transporter 1 protein (ctr1p), are part of same genes regulatory network and are reciprocally regulated at the transcriptional level by the feedback mechanism that is dependent on copper concentration gradient levels modulated by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts. Glutathione (GSH) genes lie up-stream in this genes regulatory network that modulates the recombination potentials, genomic variation and indirectly influences the biosynthesis of intracellular cholesterol. When cells experience an injury, biological damage or physical distortion leading to generation of enhanced oxidative fluxes which disturb homeostasis that in turn shifts metallic ions balance, oxygen and energy demand, pH, etc. altering functional dynamics of the cells. This disturbance can disrupt pH buffering systems and drive the each cell into an altered state of activity, reflecting transformation in cellular structure and functions. These persistent changes can initiate neurodegenerative diseases when these transformations occur in the brain tissues where as in other parts of the body these changes can cause onset of a wide range of non-contagious diseases. The outcome depends on the key players such as diet, environmental conditions and mental wellbeing, as well as on regeneration and repairing capacities of the body. These drivers also influence innate biological, biochemical, physical and genetic make-up as well as their network of pathways that govern or driving these processes. The entire system functions in coordination across the biological evolutionary linkage web, that includes the roles of biologically poorly classified and controversial entities such virus and prions. These entities can cumulatively influence genomic, epigenomic and extra-genomic regulation, effecting the activity of the *SOD1* that encodes for Cu-Zn superoxide dismutase (sod1p)-*CTR1* that encodes for membrane copper transporter 1 protein (ctr1p) genes regulatory network through copper concentration gradient levels modulated by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts. The shifts in ionic concentrations, reflected as ongoing fluctuations in oxidative stress fluxes intensity and their dispersion, altering the binding potentials of chemical ligands and other chemically and biochemically active entities, their respective and cumulative roles and the targets in the individual cells. These changes can extend to tissues and even up to physiological systemic levels, affecting cell phenotypes; their recombination and biological potentials in addition to affecting their genomic makeup conservation. This can also influence evolutionary flexibility facilitating integration of biological entities within a given ecosystem and across multiple diversified ecosystems. As an outcome of existing genomic homology across the web of life evolutionary linkage tree, biologically originated organic food helps to maintain natural health by supplementing the ongoing nutritional deficiencies occurring at cellular levels, protecting the body from diseases onset by augmenting their innate physiological features and immunological potentials [4-22,27-30,38,42,43,45-48,50,53,55-66,69-156].

Shared genes regulatory networks drive the effectiveness of identical food preparations against the different illnesses

According to the literature, many illnesses share the same physio-pathological pathways' cascades driven by partially common regulatory genes' networks. Therefore, the same food therapy, including the use of specific food preparations, is proven effective against a wide range of diseases. This finding supports the hypothesis derived from the study of Rab, 2007 which has been further elucidated through alternative scientific narratives.

The effects of COVID 19 virus on the human brains are similar to those observed in Alzheimer s' disease confirming that in many diseases, the status of mental health depends on sustainable supply of adequate copper levels and its availability at target sites. Any shift in copper ions availability in turn influences cellular respiration, alters cellular energy demand that can shift cellular dynamics to other genetically and/or epigenetically pre-programmed metabolic provisions which in turn generally enhance oxygen demand and bioenergetics of the cells across the tissues, effecting ongoing physiological systemic operations within the living organism. This modulatory mechanism alters cell cycle events, influencing cellular aging, regeneration and adaptation potentials across the biological entity. These findings confirm the key role of holo-Cu-Zn superoxide dismutase (holo-sod1p) such as (Cu(2+)loaded molecular form possessing enzyme activity) molecules and apo-Cu-Zn superoxide dismutase (apo-sod1p) such as (Cu(2+) deficient molecular form lacking enzyme activity) molecules in regulating molecular events, governing their functions by involving co-ordination chemistry principles in response to environmental changes occurring intracellularly and intercellularly in their environment [4-22,27-31,38,42,43,45-48,50,53,55-72,74-89,92-96,98-101,105-113,115,127-133,135-182].

Changes in environmental variables drive shifts in the microbial populations' dominance

The human body harbors a mixed population of microorganisms competing for survival. As discussed earlier, shifts in the cell populations and their cell phenotypes, adaptability and virulence factors, particularly in deep wounds in immunocompromised individuals, cumulatively contribute in altering the antibiotic resistance, immunity status of these individuals. This process occurs through underlying mechanisms of coordinated and interconnected processes linked to the operation of genes regulatory networks that drive genetic and/or epigenetic modulation of cellular events. These shifts are often driven in response of augmented oxidative fluxes regeneration, that alter oxygen demand and bioenergetics influencing respiration modes, homeostasis cellular requirements and potentials of the different cell populations and micro-organisms, effecting their recombination potentials and genomic makeup conservation. These factors define their biotic relationships in a given ecosystem, where abiotic and biotic factors interact, evolve and transform overtime, contributing to ongoing shift in microbial cell populations' dominance in the ecosystem. Universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch a key role in modulating these dynamics, mainly driven by Cu-Zn superoxide dismutase (sod1p) molecules' stereochemistry, shifts in the enzymatic roles in addition to universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch's indirect involvement in the genes regulatory networks that control microbial interactions, their survival, effecting their recombination potentials and genomic makeup conservation [3-8,10-22,38,42,43,46-48,50-52,55,56,58,61-66,70-72,74,75,78,80,82,85-87,89,90,93,94,96,97,99-101,103-107,109-116,127-136,138-140,146-155,158-162,167,175-179,181-187].

Copper levels modulated by copper-iron associated and dissociated ionic equilibrium balance gradient and *SOD1-SOD1* gene product Cu-Zn superoxide dismutase (sod1p)-A common connection of pathways between contiguous and non contagious diseases

COVID 19 virus affects human brain in a manner similar to that of Alzheimer's disease, confirming that diseases are influenced by the shifts in the copper levels modulated by copper-iron associated and dissociated ionic equilibrium balance gradient and by the sustainable supply of adequate copper levels to nourish target moieties across the living entity. Any shift in copper ions availability in turn influences cellular respiration, alters cellular energy demand that can shift cellular dynamics to other genetically and/or epigenetically pre-programmed metabolic provisions which in turn generally enhance oxygen demand and alter bioenergetics of the cells across the tissues, modulating the evolution and survival of various cell phenotypes and their functional potentials across the tissues affecting

the functions of the brain like and unlike other tissues composing the organs interconnected by physiological systems in a given living entity. These changes cumulatively influence physiological systemic operations of a given living entity besides extending across the biological networks effecting recombination potentials and genomic makeup conservation. These findings highlights the key roles of the holo-Cu-Zn superoxide dismutase (holo-sod1p) such as (Cu(2+)loaded molecular form possessing enzyme activity) molecules and apo-Cu-Zn superoxide dismutase(apo-sod1p) such as (Cu(2+) deficient molecular form lacking enzyme activity) molecules in regulating molecular activities, mediated by involving co-ordination chemistry principles that responds to environmental changes intracellularly and intercellularly across their ecosystem. As stated earlier, the alternative scientific narratives, derived from the study conducted by Rab (2007), explains the mechanisms underlying shifts in microbial populations, cellular phenotypes adaptability and virulence. These phenomena are particularly observed in deep wounds in immunocompromised individuals where ongoing changes alter antibiotic resistance, immune status, regenerative capacity and overall health. These interconnected and co-regulated mechanisms underlying biological events are closely linked to genes regulatory network existing between *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) and *CTR1* gene that encodes for membrane copper transporter 1 protein (ctr1p) which functions in copper levels dependent manner, modulated by copper-iron associated and dissociated ionic equilibrium balance gradient. This copper-dependent regulatory mechanism driven pathways modulated by oxidative stress shifts, acts as a common underlying phenomena, governing cellular events essential for aging, adaptability, respiration modes' selection, energy demands' shifts and cellular pre-death events leading to apoptosis, ferroptosis, necrosis etc. It also regulates microbial infectivity, selective resistance to antimicrobial agents and interactions with other biotic factors in the ecosystem which in addition to varying, evolve and transform over time, effecting recombination potentials and genomic makeup conservation.

Universal evolutionary capacitor

According to Bergman and Siegal (2003) evolutionary capacitors suppress phenotypic variations under normal conditions but revert these variations when functionally compromised; particularly under environmental stress conditions. This phenomenon is accompanied by causing pleiotropic effects on the key developmental processes. Literature confirms the presence of a universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch. It is uniquely positioned as the only known regulatory transcript that effectively functions within genes regulatory networks, across heterogeneous and homogeneous diploid cells, haploid cells and in gametes. It also plays a pivotal role in modulating cellular fate by regulating the evolution of environmentally tailored cellular phenotypes in response to augmented oxidative fluxes' bursts. These modulatory phenomena are genetically and/or epigenetically driven indicating the key role of *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) in cellular adaption, evolution, integration and survival effecting recombination potentials and genomic makeup conservation. Despite its prominence, I did not include this discovery in my research thesis which I submitted in 2007 to the University of Nottingham, United Kingdom under supervision of My Research Teacher. I omitted it at the request of My Research Teacher [9-22,38,82,83,126-132,185-187].

Shifts in the multifaceted role of chemical entities and cellular organelles under non-physiological and unusual cellular environment-oxidative stress

Overall the literature offers an alternative narrative explaining shifts in gene networks operations are modulated by interdependent levels of metallic ions particularly those of iron and copper ions and their sustainable supply. These shifts are crucial drivers of aging associated changes, primarily through shifts in stereochemical equilibrium and enzymatic roles of biomolecules such as Cu-Zn superoxide dismutase (sod1p). Changing in pH buffering capacity, intracellulary, intercellularly and in the outer environment, affects cell membrane's potentials and the selective permeability, particularly making the cell vulnerable. According to author's findings [16,17] and those of

Bishop., *et al*. 2007, decrease in Cu-Zn superoxide dismutase (sod1p) activity, its dismutase activity shift to peroxidase activity are a few features which are generally demonstrated under non-physiological and unusual conditions and under certain illnesses like in cancer coupled with stereochemical shifts, those are central to process of aging. The role of *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) in driving the evolution of well adopted cellular phenotypes and their survival diminishes when gene or genes including *GSS* gene encoding glutathione synthetase involved in glutathione (GSH) synthesis is/are deleted, preventing the production of glutathione (GSH). Glutathione (GSH) synthesis is essential for cell viability because the enzyme activity of Cu-Zn superoxide dismutase (sod1p) decreases with aging, with or without showing any considerable change in its levels. Cu-Zn superoxide dismutase (sod1p) enzymatic activity diminishes with the absence of glutathione (GSH), that is not dependent on *Lys 7/CCS* gene product (*Lys 7/CCS* gene product that delivers copper ions to apo-Cu-Zn superoxide dismutase (apo-sod1p) such as (Cu(2+) deficient molecular form lacking enzyme activity) molecules when *CTR1* gene encoding for membrane copper transporter 1 protein (ctr1p) is turned on. Glutathione (GSH) levels decrease with age. Glutathione (GSH) levels modulate intracellular copper and iron ions balance dynamics, driving cellular bioenergetics shifts, effecting oxygen demand, altering respiration modes in response to localized or physiological systemic injury. The underlying mechanism of this phenomena contributes to weaken the oxidative stress buffering systems which is manifested as intracellular and intercellular pH fluctuations leading to evolution of genetically and/or epigenetically pre-programmed or un-programmed well adopted cellular phenotypes with altered operational and functional dynamics. These phenotypic adaption's effects, whether transient or long lasting, play prime role in augmenting epigenetic based roles' share in altering genetically or non-genetically programmed processes. These processes include environmentally triggered shifts in cell physiology, biochemistry and spatial orientation which in turn may trigger pathological pathway cascades driving the cells to undergo unusual cellular events. For example, shifts in cell bioenergetics mediated by genetic, epigenetic or non genetic regulatory operations alter biochemical equilibrium. These changes modify the characteristic features and functions of biomolecules sometimes without appearing clear disease symptoms or any noticeable indication. In broader prospects these findings confirm the key role of *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) in cellular adaption, evolution, integration and survival, effecting their recombination potentials and genomic makeup conservation [4-22,27-30,38,40-43,45-53,55-66,69-81,83,84-89,91,93-101,103-116,126-155,157-162,165-167,169-173,175-187].

Insulin independent sugars can enhance cellular adaptability and evolutional potentials

Sterol Regulatory Element Binding Protein-1 (SREBP-1) is a transcription factor that regulates lipid synthesis by controlling the expression of genes involved in cholesterol and fatty acid metabolism. In human tissues, sterol regulatory element binding protein-1 (SREBP-1) transcription factors are the principal mediators of insulin action effecting expression of SREBP-1c (sterol regulatory element-binding protein 1c) that is a transcription factor that plays a major role in regulating the expression of genes involved primarily in the synthesis of fatty acids and triglycerides, particularly in the liver and adipose tissues [135-140].

The roles of insulin-oxidative stress

The roles of insulin in the body are influenced by oxidative stress acting at both the cellular and physiological systemic levels This modulation is dictated by the types of dietary components intake, particularly sugars that define maintenance of intracellular and intercellular homeostasis. Key players, such as sustainable supply and availability of oxygen and metallic ions, (particularly that of copper and iron) and cell bioenergetics govern tissue functions; play a critical role in shaping physiological processes and directly and indirectly affecting the roles and actions of insulin. These processes regulate body functions across the physiological systems, which are differently modulated in brain tissues, heavily influenced by the types of fate opted by the cell populations and by the key players, modulating the cells fate options which are altered on onset of certain diseases [4-22,27-30,38,40-43,45-53,55-66,69-81,83-89,91,93-101,103-116,126-155,157,159-162,165-167,169-173,175-187]. Research indicates that modes and rate of respiration, bioenergetics and homeostasis can considerably vary from cell to cell and within the same cell over time. These variations are influenced by free oxygen availability, metallic ions and electrolytes balance shifts, nutrient types, dietary factors and by the exposure to infectious or noninfectious

immunogens, among many other driving players. These driving players exert a wide range of effects on the bodily functions, particularly those involving the brain or occur within the brain and/or in nervous system. It includes appearance of a common pathological feature in response of distorted homeostasis leading to the formation of plague like structures composed of cell debris in vessels, in tissues of brain and in other organs, escaping the death events in response of enhanced cell-to-cell variability, that is one of the consequences of hemoglobin molecules driven oxidation particularly targeting cell membranes' cholesterol structure on release of free iron in response of heightened oxidative stress [4-22,27-30,36,38,40,42,43,45-48,50-53,55,56,58-67,69-81,83-89,91-94,96-101,104-116,126-155,157-164,166-169,172,173,175-178,185-187].

Interplay of universal evolutionary capacitor switch (*SOD1*-sod1p) and ionic and non ionic chemical entities balance shifts in the different cell types

Previous studies highlight unconventional mechanisms that drive the phenomena underlying cell physiological and pathophysiological events. These events are intertwined with cellular adaptability and regenerative potentials, profoundly influencing the aging process. Overall, the multifaceted strategies employed by individual cells and their assemblies within tissues as well as their interactions with the environment, shape systemic physiology and define the cellular phenotype of a given biological entity. Regardless of diversity in the genetic makeup and the cell machinery, shifts in oxidative stress appear to influence the key drivers linking biotic and abiotic variables in a given ecosystem. This modulatory network influences individual cellular phenotypes their functional potentials, primarily through universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch which in turn define the roles and targets of other chemical and biochemical molecules and their associated ligands in a given the scenario.

Generally the composition, functionality and operations of the cell systems, both at the individual cell levels and at the individual organ levels, are interconnected through systemic tissues networks. Typically, brain exhibits distinct responses to any inadequate supply of metallic ions and free oxygen, varying with the type of sugars consumed regularly. This inadequacy affects normal physiology and manifests as behavioral changes, influencing psychological outcomes. These changes may trigger genetic, epigenetic and non genetic regulatory pathways cascades shifts which may in turn induce neurodegenerative diseases onset in epigenetically and/or genetically regulation dependent or independent manners. These ongoing processes are also regulated by epigenetically interconnected networks involving metallic ions and free oxygen sustainable supply, respiration mode and bioenergetics shifts and types of consumed food affecting the sugars' supply etc. altogether influencing natural health. Metallic ions which play key role in driving these processes are generally transported and trapped by sequestration with ligands. Food is a good source of different biomolecules that can trap and/ or carry metallic ions passing across the biological barriers such as blood-brain barrier transporting them to brain cells and also across the other targeted cells effecting their activities in the body [4-22,27-31,38,42,43,45-50,54-66,69-81,83-89,91,93,94,96-102,104-116,126,128,130-145,147-155,159-164,166,168-170,172,173,176-178,182-187].

Dual roles of *SOD1*-Sod1p-a common universal evolutionary switch complex or a universal evolutionary capacitor switch

Universal evolutionary capacitor also functions as a component of common evolutionary switch, operating as universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch. Its role is evident across the phylogenetic spectrum of living organisms, both within evolutionary linked interconnected biological networks and across the distantly related or unrelated biological systems. As mentioned earlier, universal evolutionary capacitor also functions as a component of common universal evolutionary switch, operating as universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn

superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch which is regulated at the level of genes operation networks and is intrinsically linked to be governed by oxidative stress shifts modulating normal cellular and physiological systemic functions. These oxidative stress shifts can be triggered in cells in response to any intracellular event such as exposure to an infectious agent in epigenetically and/or genetically pre-programmed manners or can be triggered by external stimuli. These responses may also be launched in epigenetically and/or genetically pre-programmed or un programmed manners or such as by facilitating the evolution of entirely novel biological constructs for which no naturally evolved pre-programmed paradigm exist, driving cells to launch diversified unusual responses with genes' networks and metabolic cascades functional on altered framework as it is demonstrated in the case of COVID19 virus infection driven manifestations. For instance in case of COVID19 virus driven manifestations, COVID19 virus acting as an unanticipated external stimuli disrupts physiological systemic homeostasis, compelling the body cells to adapt by evolving cells with well-tailored phenotypes that function on altered framework. These cell phenotypes existing within infected patients can be better suited to the altered environment conditions and can emerge with or without altering oxygen demand, modes of respiration cell bioenergetics and other characteristic features. This adaptability influences the onset of diseases within infected individuals which may be diversely demonstrated in genetically varied counterparts. Therefore understanding of these phenomena underscores the finding that the long-term consumption of biologically derived natural food can influence disease onset, progression and cure a concept that will be elaborated upon in later sections [4-22,29-31,35,38-43,45-72,74-81,83-89,91-178,182-187].

When external environmental drivers change or organisms or cells are exposed to uncommon or unusual stimuli as a response, shifts in their physiological systems effect genetically, epigenetically and non genetically controlled cellular functions, altering their activity which in turn triggers the evolution of new cell phenotypes with altered characteristic features. These new cell phenotypes may carry adaptive capacities evolved beyond their natural genetic and epigenetically regulated pre-programmed framework ultimately influencing the structures and functions of tissues, physiological systems in addition to effecting the roles and targets of chemical and biochemical species in various yet-unrevealed manners [4-22,27-31,35,38-41,45-48,50,54,55,58-72,74-81,83-89,91-101,104-107,110-116,126-178,182-187].

Common universal capacitor evolutionary switch or universal evolutionary capacitor and the climate change

Climate has a global impact on adaptability and potentials of biological entities. When environmental conditions change organisms become more flexible to adaptation, fostering evolutionary transitions. Weakly virulent species may evolve into potent biological threats, driving the emergence of new pathologies and diseases. These changes may result in enhanced resistance against antibiotics, varying effects of medication are demonstrated across different regions over time. Climate change can induce emergence of novel diseases and syndromes based challenges. Climate driven deviations from natural-lifestyles and practices exacerbate these challenges. For example, reduced availability of free molecular oxygen, shift in natural microbial flora populations are found to occur even in the open fields. Limited exposure to sunlight and to fresh natural air enhances adverse effects of climate change on physiological systems that inherently harm natural health.

Obsolete interpretations

Practical implications

SOD1 is a gene that encodes for Cu-Zn superoxide dismutase (sod1p) molecule, carrying copper and iron as co-factors, is responsible for antioxidant enzyme activity under physiological conditions and for peroxidase activity under non-physiological and unusual conditions or in certain diseases such as in cancer. *CTR1* gene, which encodes for a high-affinity membrane copper transporter1 protein (ctr1p) and *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) lie within the same genes regulatory operation network. These genes are reciprocally regulated at transcriptional level in copper concentration gradient levels dependent manner modulated

by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts through feedback mechanism. Upstream in this genes regulatory network is gene or genes including *GSS* gene encoding glutathione synthetase involved in glutathione (GSH) synthesis which indirectly regulates intracellular cholesterol biosynthesis and effect modes of respiration and cellular bioenergetics. This interplay governs cellular pH and homeostasis status cumulatively modulating the operations of genes' regulatory networks. This dynamic web of networks presents various pre-death cellular options and options to escape death naturally or in response of any stimuli, injury or biological event by evolving as new cell phenotypes with or without undergoing pre-mature aging process. These processes enable cells to adapt, survive and proliferate producing daughter cells with altered potentials and roles in the tissues, organs and systems. Shifts in coordinated balance of copper and iron supply can affect the multifaceted functionality of a universal evolutionary capacitor that also functions as a component of common universal evolutionary switch operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch. These disturbances can alter the stereochemistry of Cu-Zn superoxide dismutase (sod1p) such as transitioning between holo-Cu-Zn superoxide dismutase (holo-sod1p) (Cu(2+) loaded molecular form possessing enzyme activity) molecules and apo-Cu-Zn superoxide dismutase (apo-sod1p) (Cu(2+) deficient molecular form lacking enzyme activity) molecules, can alter their enzymatic roles effecting ligands' sequestration potentials. This disruption serves as a central switch that can initiate the onset and drive the progression of illnesses particularly non-contagious diseases, including metabolic syndromes, neurodegenerative diseases, prion manifestations and contagious diseases such as bacterial, viral and parasitic infections and other manifestations such as antibiotic resistance, infarctions and stokes etc. [82,167,178-181,183-187].

Fresh unpeeled produce and food products derived from biological natural sources, that are minimally processed by using traditional methods for natural fermentation and by applying natural preservation techniques when are used regularly, can play a key role in suppressing the severity of diseases in addition to preventing their onset. Food is a rich source to provide loaded Cu-Zn superoxide dismutase (sod1p) (carrying copper and zinc attached to apo-Cu-Zn superoxide dismutase (apo-sod1p) molecular form possessing enzyme activity) molecules to the body and can play a critical role in protecting the body against various illnesses and modulates their onset, progression and recovery. At the first signs of stoke, consuming food rich in bioavailable copper attached with carrier molecules capable of passing across the biological barriers including blood brain barrier can potentially disrupt biological pathways' cascades responsible for stroke related manifestations. A specific example is consuming non-spicy chilli and capsicum meat curry prepared with naturally whole fat fermented yogurt in traditional manner, desi Pakistani meat curry [35,39,40,186] in time can nullify the neurological consequences of stoke confining the effects only to temporary muscular weakness.

Many natural dietary preparations can be used for treating illnesses that are currently deemed incurable. These dietary preparations facilitate complete recovery without causing complications or side effects. Certain food preparations played a vital role in eradicating COVID19 pandemic. These food preparations have contributed to global efforts toward mitigating the COVID 19 pandemic's impact, safeguarding the health and well-being of communities worldwide while recognizing the potentials of food therapy as one of the key natural health-supporting interventions.

According to Rab (2007) enzymes do not play a direct role in the onset, progression and cure of many diseases, including neurodegenerative disorders. These findings contradict with much of literature reported in related fields, such as the medical sciences, food sciences, business and the allied fields. They also raise serious concerns regarding the credibility of the findings reported by Schlessinger., *et al*. (2011) who had described a mutual relationship existing among protein dysfunctions, cell survival and disease.

Practical implication and limitations-diagnostic imaging

Diagnostic imaging of organs, particularly those related to brain physiology and pathology can result in misleading interpretations. These misinterpretations are primarily based on attributed variation in molecular pathways circuits as well as the selective permeability

and filtering properties of biological barriers including blood brain barrier which regulates the accessibility of biomolecules. The body physiological systems and their regulation at molecular level are influenced by homeostasis shifts, dietary composition and intake frequency that may preserve normal physiology but with appearance of changes in the morphology, demonstrated in diagnostic images, a commonly observed feature but remains unexplained on logical and scientific grounds. Certain dietary preparations have been proven to play a key role in eradicating the COVID19 pandemic worldwide.

Universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch that in addition to other characteristic features, represents the only regulatory transcript that is equally functional across various genes regulatory networks, modulating the shifts in their functional networks. These networks operate both in heterogeneous and homogeneous diploid cells, haploid cells and in gametes modulating the cellular fate and regulating the evolution of environmentally well-tailored cellular phenotypes that are generally triggered in response to oxidative fluxes' shifts. As already mentioned earlier, despite its prominence, I did not include this discovery in my research thesis which I submitted in 2007 to the University of Nottingham, United Kingdom under supervision of My Research Teacher. I omitted it at the request of My Research Teacher [126,185-187].

The image does not necessarily illustrate the biological processes occurring at molecular levels which are responsible for defining a given health or disease spectrum. As already mentioned earlier these misinterpretations are primarily based on attributed variation in molecular pathways' circuits as well as the selective permeability and filtering properties of biological barriers including blood brain barrier which regulates the accessibility of biomolecules. The body's physiological systems and their regulation at molecular levels are influenced by homeostasis shifts, dietary composition and intake frequency that may preserve normal physiology but with appearance of changes in the morphology, demonstrated in diagnostic images, a commonly observed feature but that remains unexplained on logical and scientific grounds.

Given the aforementioned reasons, the interpretation of diagnostic images has lost its authenticity; therefore a critical peer review of the work published over the last two decades in areas such as medical sciences, food sciences, business studies and the allied fields is necessitated. In addition to, the current understanding within these domains of knowledge as well as their integration and application should be revised to address the challenges of the present era and the future. These efforts are essential for ensuring the safety and well-being of the global community and for promoting natural health for current and future generations.

Striking feature

According to the literature, iron and copper homeostasis and their crosstalk coupled with oxidative stress fluctuations and intracellular pH shifts, play a pivotal role in modulating cellular functions and responses. These responses extend across tissues and physiological systems, influencing immunological reactions and their impact on the host's body. Cellular and physiological systemic responses mostly involve universal evolutionary capacitor either directly or indirectly that also functions as a component of common evolutionary switch, enjoying key regulatory role by operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch either directly or indirectly that also functions, in parallel as a component of universal evolutionary capacitor switch complex acting as a junction, which governs various metabolic pathways' cascades in diverse manners, varying from illness to illness.

Food is a rich source to provide loaded Cu-Zn superoxide dismutase (sod1p) (carrying copper and zinc attached to apo-Cu-Zn superoxide dismutase (apo-sod1p) molecular form possessing enzyme activity) molecules to the body and can play a critical role in protecting the body against various illnesses and modulates their onset, progression and cure.

Septicemia, tuberculosis (including miliary tuberculosis), listeriosis, *Naegleria fowleri* infection and conditions such as heart failure, diabetes, Drown syndrome, amyotrophic lateral sclerosis (ALS), Parkinson' s disease, prion diseases and viral infections can be mitigated, even if not prevented, by restoring the disrupted copper and iron balance driven homeostasis and their beneficial cross talks, in addition to, by buffering any sustainable shifts in intracellular and intercellular pH and oxidative stress governing homeostasis's stability, cumulatively effecting the cellular functions and their connectivity with the environment. These outcomes can be technically facilitated through various medical strategies [82,167,178-181,183-187] or by means of administering appropriate diet preparations [35,39,40,186] alone or as an adjuvant therapy, such as food therapy.

When naturally fermented mustard infused chilli pickles are consumed along with or without COVID 19 specific diet preparations, or with other dietary preparations originated from natural biological sources including those reported by the author [35,39,40,186] regularly, with or without drugs including antimicrobial agents, they can promote rapid recovery while minimizing the risk of side effects and without causing long-lasting complications. Utilizing these dietary preparations and their combinations can be beneficial in protecting against many diseases because responses against a wide range of diseases are mediated by partially shared biological pathways' cascades regulated by a common universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch, either directly or indirectly that also functions, in parallel, as a component of universal evolutionary capacitor switch complex, acting as a junction, which governs various metabolic pathways' cascades in diverse manners, varying from illness to illness. This common universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch is also present and is functional across phylogenetically linked, related and unrelated biological entities and relates with accidently evolved or deliberately constructed biological threats. This is for the same reason dietary preparations active against flu virus infection are also found effective against COVID 19 virus driven illness manifestations. These dietary preparations also modulate intracellular, intercellular and cell surface manifestations, mostly by involving cell membranes, thereby altering infection-acquiring potentials. This approach represents a novel strategy for treating more challenging diseases, such as tuberculosis, COVID 19 and other viral infections, prion diseases, neurodegenerative diseases and many other diseases leading to complete cure.

Bitter fact

Many individuals worldwide, naturally deviates from assigned standards categorizing health profiles, primarily as a consequence of their altered genes regulatory circuits. These differences in their biological network designs and their integrated regulation confer distinct health features, as an outcome of varying biological pathways networks particularly creating more profound effects by epigenetically regulating genes functionally connected with other genes constituting other regulatory networks. Consequently individuals who are typically classified abnormal, eventually categorized medically as healthy individuals having normal abnormality spectrum. These variations necessitate introducing individualized treatment strategies with drug doses tailored to unique epigenetic framework of each individual governing the mechanisms underlying regulatory biological processes' framework and the responses driven by them individually or cumulatively govern the outcomes of mutations, family tree linkage, etc. Hence, the standard of normality is regarded

as a varying index differing from individual to individual depending on each individual's family geographical origin, relocation history, infectious illnesses history, a list of allergens they are sensitive to, in addition to, other information related to each individual, all of which may contribute to an individuals comprehensive medical history.

Buffering shifts in intracellular and extracellular ionic concentrations, homeostasis, pH levels, oxidative stress and osmotic stress levels demonstrate alternative strategies for the primary treatment and adjunctive treatment of a wide range of contagious and non-contagious diseases including tuberculosis, COVID19 driven illness manifestations, and other viral infections, prions manifestations, neurodegenerative diseases including Amyotrophic Lateral Sclerosis (ALS) etc. potentially leading to complete cure.

This approach, which has recently emerged in medical sciences, offers a novel paradigm in diseases management. For example, oral administration of mustard oil based naturally fermented pickles with antibiotics may aid in eradicating infections, particularly those leading to septicemia.

Overall, the implications of insufficient knowledge in medical sciences have placed individuals at risk, particularly those with altered standards of health spectrum, by prescribing unnecessary treatments or conducting medical procedures not suited for them. These actions, while intended to aid the patients, are often driven by a desire to generate data for academic publications or to facilitate the development and marketability of commercial products. The major content built from this type of research is based on inaccurate and incomplete knowledge understandings, leading to proliferating practices that, instead of enhancing patients well being, contribute to promoting ineffective, unnecessary or harmful treatments and unnecessary use of diagnostic tools and tests on patient s samples without taking their consent to use the findings in research publications. Findings of substandard research are never reliable enough to secure the investments made on projects based on them, making the approach to link academia with industry a risky strategy.

SOD1 and autism linkage: An alternative scientific narrative

Autism, a prevalent disorder of contemporary society, is commonly characterized by difficulty in sustaining attention, alongside other cognitive and behavioral impairments [188-190]. A key factor underlying the autism severity depends on types of sugars utilized by the body particularly insulin dependent sugars (which requires insulin for absorption in target cells), that sharply shift glycemic index when administrated in concentrated form particularly in form of soft drinks and juices. These sugars which are absorbed in targeted cells exhibit considerable shift in glycemic index and contributing to lasting sharp fluctuations in the blood glucose levels and oxidative stress. By contrast, insulin independent sugars, which enter target cells without requiring insulin do not induce a major shift in glycemic index. These sugars, when they are consumed can be metabolized through the glycolytic pathway without directly involving electron transport chain driving the cells to attain stable oxidative state when are consumed at low concentration levels. In case of glucose, which is primarily metabolized by glycolytic pathway and associated with electron transport chain, the metabolic reactions are coupled with release of intense oxidative bursts. These oxidative bursts heighten oxidative stress which in turn can disrupt the synaptic release of glutamine, a critical neurotransmitter required for normal brain functions. This disruption hinders the communication among different brain regions that regulate behavior, particularly in context of the neuromuscular junctions involved in neuromuscular transmission, adversely effecting the focusing potentials and duration [4-22,27-31,33,38,43,45-48,50,53,55,56,58-66,69-72,74-81,83-95,97-102,104-110,112-116,126-166,168-173,175-182,185-190].

Children with autism may experience a reduction in intensity of their symptoms if they are taught to address their deficiencies while consuming meals that include raw vegetables with peel, naturally fermented foods, home-made chutney with traditional Pakistani food [35,39,40,186] freshly prepared, by using fresh natural ingredients of biological origin in the open air, ideally in sunlight, particularly during early stage of their lives. Fermented foods are a rich source of probiotics and biologically active molecules with multifaceted roles, generally capable of passing across biological barriers including the blood brain barrier to deliver the essential biochemical or chemical entities to the target cells.

Under non physiological or unusual cellular conditions, cells may deviate from their innate functions. Free oxygen demand, mode of respiration, cellular bioenergetics, dietary requirements and other characteristic features can vary and alter over time. Under unusual or non-physiological conditions the naturally assigned roles of food ingredients can also alter. They also appear to traverse biological barriers present throughout the living organisms, that are built of cell layers forming tissues and organs connected through physiological systems thereby maintaining selective permeability between inner and out environments partitioned by biological barriers in the body [34,35,37,39-41,50,69,76,88,92,126,168,172,182,183,185-187].

Adding pink Himalayan salt to food can pose unidentified and potentially fatal risks, particularly for individuals on medication, especially for those on medications affecting nerves, brain and behavior. Similarly hyper-processed commercially prepared food items that contain additives and preservatives, particularly chemically synthesized ingredients, can be highly detrimental to both physical and mental health undermining natural brain functions and overall well-being [37,69,76,88,92,126,168,172,182,183].

Discussion

This unconventional work presents *Saccharomyces cerevisiae* as a model that can be used as a tool for investigating biological processes including those occurring in humans at molecular levels in genetically, epigenetically and non genetically dependent or independent manners, in addition to, investigating the role of the biological processes and their responses, influencing cellular functions particularly by epigenetically modulating genes regulatory networks' operations, transmitting their impacts across the living body.

As discussed earlier, Rab (2007) reported that *SOD1* gene that encodes for Cu-Zn superoxide dismutase (sod1p) and *CTR1* gene that encodes for membrane copper transporter 1 protein (ctr1p) are part of same gene regulatory network and are reciprocally regulated in response to copper concentration gradient levels dependent manner modulated by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts through feedback mechanism at the transcriptional level. It demonstrates that physical, chemical and biochemical stimuli or an injury can alter the effects of mutations that impair the function of essential genes operating within the same regulatory network. These phenomena can enhance the activity of weaker genes. This discovery raises questions regarding the credibility of the findings suggesting that chemical and biochemical reactions including their pathways, cascades and targets always alter their functional potentials when genes are deleted. Furthermore, these findings question the credibility of traditional understanding of the relationship existing among protein dysfunction, cell survival and disease. These findings imply that cellular events are epigenetically regulated in parallel with fluctuating oxidative fluxes' generation serving as a driving stimuli, triggering the selection of cellular fates' options; cells that escape pre death cellular events, emerge as new well adopted cellular phenotypes by genetically, epigenetically and/or non genetically regulated processes' underlying mechanisms involving metallic ions and their ionic interdependencies modulating oxidative stress status, pH, sustainable oxygen supply, homeostasis, cell bioenergetics etc. Overall universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch that altogether through unusual displacement of the equilibrium of Cu-Zn superoxide dismutase (sod1p) between holo-Cu-Zn superoxide dismutase (holo-sod1p) (Cu(2+) loaded molecular form possessing enzyme activity) molecules and apo-Cu-Zn superoxide dismutase(apo-sod1p)(Cu(2+) deficient molecular form lacking enzyme activity) molecules which emerges under stress conditions modulates various metabolic events to regain physiological characteristic features thereby restoring homeostasis. Under prolonged non-physiological or unusual conditions, the universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch regulating transcripts that govern cellular adaptability, recombination compatibility and evolutionary potentials. As discussed earlier under prolonged non-physiological or unusual

conditions, the universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch that also functions in parallel as a component of universal evolutionary switch complex acting as a junction that is involved in modulating the fate of cells by conferring altered roles to chemical and biochemical entities and organelles. This epigenetically driven feature is common across web of life; it exists in phylogenetically linked, related and un-related entities as well as across the cells of functionally connected tissues and organs composing physiological systems within multicellular organisms. The stereochemistry of chemical and biochemical species effected by the roles of the universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch that in parallel acts as a functional complex serving as an index detecting changes in the external environment including climate change and thereby transmitting its impact across the cells, tissues, organs, physiological systems and their environment in the body. This phenomenon explains why various diseases both contiguous and non-contiguous share the same genes regulatory networks governing their illness and recovery manifestations. It also elucidates why the same dietary preparations are effective in preventing various diseases onset and facilitate their recovery. Hence, the standard of normality is considered as a varying index differing from individual to individual depending on each individual's family geographical origin, relocation history, infectious illnesses history, a list of allergens they are sensitive to, in addition to, other information related to each individual all of which may contribute to an individual's comprehensive medical history. Consequently, the credibility of diagnostic imagining is compromised. This work presents simple strategies for managing and curing many illnesses that are currently incurable and pose challenges to medical sciences, emphasizing the use of food preparations as naturally designed medicines for food therapy alone or as an adjuvant therapy.

Conclusion

It was reported by Rab 2007 that physical, chemical and biochemical stimuli or an injury can alter the effects of mutations that impair the functions of essential genes operating within the same regulatory network. These phenomena can enhance the activity of weaker genes. Specifically, the study revealed that *SOD1* gene, (that encodes for Cu-Zn superoxide dismutase (sod1p), a protein that binds copper and zinc ions in its molecular structure, destroys free superoxide radicals including those generated by electron transport chain (respiratory chain)) and *CTR1* gene, that encodes for membrane copper transporter 1 protein (ctr1p), a cell membrane protein that is a high affinity membrane copper transporter, are linked through the same genes operations regulatory network, and are thereby linked with other genes operations regulatory networks. These genes are reciprocally regulated at transcriptional level through feedback mechanism in response to copper concentration gradients modulated by iron-copper associated and dissociated ionic equilibrium balance gradient shifts driving the oxidative stress shifts. Under stress conditions when Cu-Zn superoxide dismutase (sod1p) restores its enzyme activity, the knock out cell populations exhibit a survival index similar to that of the wild-type populations indicating that cell survival may not always be directly linked to protein defects, as previously thought. These findings challenge the authenticity and credibility of the studies conducted to investigate the effects of mutations on biochemical pathways particularly those suggesting a link existing among protein dysfunction, cell survival and disease. When biochemical reactions' cascades function under non-physiological, unusual or stress conditions, their frameworks are altered.

Rab (2007) revealed that, under non-physiological, unusual or stress conditions, the regulation of genes networks' operational pathways and ongoing biochemical reactions modify their functional biochemical and chemical potentials, targets and consequences thereby driving the cumulative outcomes. For example, in del *CTR1* gene (that encodes for membrane copper transporter 1 protein (ctr1p)) yeast cells, when copper ions are sufficiently supplied to Cu-Zn superoxide dismutase (sod1p) by the *Lys7/CCS* gene product (*Lys7/CCS* gene is down regulated or is turned off under non-functional or in absence of *CTR1* gene that encodes for membrane copper transporter

1 protein (ctr1p)) the cell populations regain their viability proportion same as that of the wild type yeast cell populations exhibit on exposure with same strength of stressor. This restoration of Cu-Zn superoxide dismutase (sod1p) molecules' multifaceted chemical and biochemical potentials involving stereochemistry and enzymatic activity and their shifts enabling the yeast cell populations to regain their survival strength against the stressor in a manner similar to that observed in wild-type yeast cell populations. These findings question the credibility and authenticity of traditional understanding regarding the relationship existing among protein dysfunction, cell survival and disease. They also underscore the complexity of genomic operations and biochemical processes which may be governed solely by genetically or epigenetically regulated pre-programmed biochemical cascades alone or are modulated in combination by the existing parallel framework operated by environmental and dietary drivers. The roles of these drivers are influenced by universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch thereby effecting the roles of the other regulatory circuit modulators which drive evolution of healthy or unhealthy poorly adopted or well adopted cellular phenotypes influencing the trajectory of disease and recovery. The use of diet preparations designed by applying the knowledge revealed in the data reported by Rab (2007) has eradicated COVID19 pandemic across the globe. The reported data by Rab (2007) has raised questions on the credibility of Schlessinger., *et al*. (2011)'s findings which indicate the existence of mutual relationship among protein dysfunction, cell survival and disease; the hypothesis of the framework based study's findings on which Nobel Prize in Physiology and Medicine 2023 and 2024 respectively were given. This has raised questions on the prize winning findings as conclusions of the studies were drawn and reported without having adequate understanding of background knowledge such as neglecting the consequences of epigenetically driven related biological events and their interdependent impacts governed by multifaceted roles of universal evolutionary capacitor operating through universal evolutionary capacitor switch, such as *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) switch driving regulatory circuits, through universal evolutionary capacitor switch complex such *SOD1* gene encodes for Cu-Zn superoxide dismutase-Cu-Zn superoxide dismutase (sod1p) (*SOD1*-sod1p) composing switch and their outcomes determining the consequences that has later on become evident as discrepancies in findings in parallel reported and unreported studies which have been documented in the literature. As already discussed earlier, overall the implications of insufficient knowledge in medical sciences have placed individuals at risk, particularly those with altered standards of health spectrum, by prescribing unnecessary treatments or conducting medical procedures not suited for them. These actions, while intended to aid the patients, are often driven by a desire to generate data for academic publications or to facilitate the development and marketability of commercial products. The major content built from this type of research is based on inaccurate and incomplete understandings, leading to practices that, instead of enhancing patients' wellbeing, contribute to proliferating ineffective, unnecessary or harmful treatments and promoting unnecessary use of diagnostic tools and tests on patients' samples without taking their consent to use the data in research publications. Findings of substandard research are never reliable enough to secure the investments made on projects based on them, making the approach to link academia with industry a risky strategy.

Significance Statement

The findings and strategies presented in this paper have played a pivotal role in eradicating COVID19 pandemic from Pakistan and from several other regions across the globe.

Bibliography

1. Pray L. "Discovery of DNA structure and function: Watson and Crick". *Nature Education* 1.1 (2008): 100.

2. Koonin EV., *et al*. "The Baltimore classification of viruses 50 years later: how does it stand in the light of virus evolution?". *Microbiology and Molecular Biology Reviews: MMBR* 85.3 (2021): e0005321.

3. Misteli T. "The inner life of the genome". *Scientific American* 304.2 (2011): 66-73.

4. Barr MM. "Super models". *Physiological Genomics* 13.1 (2003): 15-24.

5. Poyton RO and McEwen JE. "Crosstalk between nuclear and mitochondrial genomes". *Annual Review of Biochemistry* 65 (1996): 563-607.

6. Cui H., *et al*. "Oxidative stress, mitochondrial dysfunction, and aging". *Journal of Signal Transduction* (2012): 646354.

7. Bhatti JS., *et al*. "Mitochondrial dysfunction and oxidative stress in metabolic disorders - A step towards mitochondria based therapeutic strategies". *Biochimica et Biophysica Acta. Molecular Basis of Disease* 1863.5 (2017): 1066-1077.

8. Dai DF., *et al*. "Mitochondrial oxidative stress in aging and healthspan". *Longevity and Healthspan* 3 (2014): 6.

9. Fairbrother-Browne A., *et al*. "Mitochondrial-nuclear cross-talk in the human brain is modulated by cell type and perturbed in neurodegenerative disease". *Communications Biology* 4.1 (2021): 1262.

10. King JL and Jukes TH. "Non-Darwinian evolution". *Science (New York, N.Y.)* 164.3881 (1969): 788-798.

11. Palazzo AF and Kejiou NS. "Non-Darwinian molecular biology". *Frontiers in Genetics* 13 (2022): 831068.

12. Ubeda F and Wilkins JF. "Imprinted genes and human disease: an evolutionary perspective". *Advances in Experimental Medicine and Biology* 626 (2008): 101-115.

13. Bergman A and Siegal ML. "Evolutionary capacitance as a general feature of complex gene networks". *Nature* 424.6948 (2003): 549-552.

14. Levy SF and Siegal ML. "Network hubs buffer environmental variation in *Saccharomyces cerevisiae*". *PLoS Biology* 6.11 (2008): e264.

15. Masel J and Siegal ML. "Robustness: mechanisms and consequences". *Trends in Genetics: TIG* 25.9 (2009): 395-403.

16. Faiza Abdur Rab Research thesis titled Phenotypic variation in stress resistance between individual cells in isogenic populations of Saccharomyces cerevisiae was submitted at University of Nottingham United Kingdom in 2007 which was funded by National Institute of Health (NIH) US Department of Health and Human Services whereas her Full PhD Tuition Fees was supported by Developing Solution PhD Tuition Fees Scholarship 2003 offered by University of Nottingham, United Kingdom and my boarding and lodging was supported for two years only by University of Karachi Pakistan's Overseas PhD Scholarship Scheme 2003 (2007).

17. Bishop AL., *et al*. "Phenotypic heterogeneity can enhance rare-cell survival in 'stress-sensitive' yeast populations". *Molecular Microbiology* 63.2 (2007): 507-520.

18. Rab FA. "Environmentally modulated evolution through genetic regulation information systems for biotechnology". *ISB news reports Virginia Tech* June/July (2014).

19. Sumner ER., *et al*. "Cell cycle- and age-dependent activation of Sod1p drives the formation of stress resistant cell subpopulations within clonal yeast cultures". *Molecular Microbiology* 50.3 (2003): 857-870.

20. Szabo I and Szewczyk A. "Mitochondrial ion channels". *Annual Review of Biophysics* 52 (2023): 229-254.

21. Ewald JC., *et al*. "The integrated response of primary metabolites to gene deletions and the environment". *Molecular BioSystems* 9.3 (2013): 440-446.

22. Lehner B. "Genes confer similar robustness to environmental, stochastic, and genetic perturbations in yeast". *PloS one* 5.2 (2010): e9035.

23. Schlessinger A., *et al*. "Protein disorder--a breakthrough invention of evolution?". *Current Opinion in Structural Biology* 21.3 (2011): 412-418.

24. Gauthier J., *et al*. "A brief history of bioinformatics". *Briefings in Bioinformatics* 20.6 (2019): 1981-1996.

25. Verma AS., *et al*. "Biotechnology in the realm of history". *Journal of Pharmacy and Bioallied Sciences* 3.3 (2011): 321-323.

26. Korf BR. "Integration of genomics into medical practice". *Discovery Medicine* 16.89 (2013): 241-248.

27. Maldonado KA and Alsayouri K. "Physiology, Brain". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing (2025).

28. Holmes GL and McCabe B. "Brain development and generation of brain pathologies". *International Review of Neurobiology* 45 (2001): 17-41.

29. Meldrum BS. "Glutamate as a neurotransmitter in the brain: review of physiology and pathology". *The Journal of Nutrition* 130.4S (2000): 1007S-1015S.

30. Aschner M., *et al*. "Metallothioneins in brain--the role in physiology and pathology". *Toxicology and Applied Pharmacology* 142.2 (1997): 229-242.

31. Mysiris DS., *et al*. "Post-COVID-19 Parkinsonism and Parkinson's Disease Pathogenesis: The Exosomal Cargo Hypothesis". *International Journal of Molecular Sciences* 23.17 (2022): 9739.

32. Rab FA. "Eat fresh live young". *EC Nutrition* RCO.01 (2017): 03-05.

33. Rab FA. "Is sugar an accessory or a necessary". *EC Nutrition* 13.4 (2018): 236-237.

34. Rab FA. "Drug disease relationship and the role of food in healthy living". *EC Nutrition* 13.8 (2018): 543-548.

35. Rab FA. "Genome-nutrifortified diets-their disease protection and remedy potential". *Journal of Probiotics and Health* 6 (2018): 204.

36. Rab FA. "Comparison between safety risks associated with domestically processed food and commercially manufactured processed food across the food supply chain". *EC Nutrition* 14.5 (2019): 414-416.

37. Rab FA. "Is hunger more dangerous than having mal-nutrition or consuming unsafe diet". *EC Nutrition* 14.12 (2019): 01-05.

38. Rab FA. "Halal or Haram-new challenges for religious scholars Muslim world and food supply chain stake holders". *International Journal of Nutritional Science and Food Technology* 6.3 (2020): 3.

39. Rab FA. "Food items biologically tailored to meet nutritional deficiency challenge during Covid 19 Pandemic". *Journal of Probiotics and Health* 9 (2021): 233.

40. Abdur Rab F and Hassan A. "Tourism, health promoting food domain and technology applications: individual's genes reservoir, environmental change and food in natural health context". In: Hassan, A. (eds) Handbook of Technology Application in Tourism in Asia. Springer, Singapore (2022).

41. Rab FA. "Would science knowledge, food and agriculture sector be considered basic human services or commercial services in this post covid19 era? decision will determine the destination". *EC Nutrition* 18.10 (2023): 01-08.

42. Bich L., *et al*. "Understanding multicellularity: the functional organization of the intercellular space". *Frontiers in Physiology* 10 (2019): 1170.

43. Freedman JH., *et al*. "The role of glutathione in copper metabolism and toxicity". *The Journal of Biological Chemistry* 264.10 (1989): 5598-5605.

44. Faiza Abdur Rab. A comparative study of immunological protection conferred by certain antigenic preparations of *Listeria monocytogenes*. MSc thesis supported by University of Karachi s departmental grant funding for post graduate research submitted to Department of Microbiology, University of Karachi, Pakistan (1995).

45. Bendjilali N., *et al*. "Time-course analysis of gene expression during the *Saccharomyces cerevisiae* hypoxic response". *G3 (Bethesda, Md.)* 7.1 (2017): 221-231.

46. Harris N., *et al*. "Overexpressed Sod1p acts either to reduce or to increase the lifespans and stress resistance of yeast, depending on whether it is Cu(2+)-deficient or an active Cu,Zn-superoxide dismutase". *Aging Cell* 4.1 (2005): 41-52.

47. Abudugupur A., *et al*. "Severe reduction of superoxide dismutase activity in the yeast *Saccharomyces cerevisiae* with the deletion or overexpression of GTS1". *FEMS Microbiology Letters* 223.1 (2003): 141-145.

48. Eberechi N., *et al*. "Perspective of bioenergetics theory of aging". *Journal of Biology and Nature* 15.1 (2023): 53-56.

49. Avery SV., *et al*. "Copper toxicity towards *Saccharomyces cerevisiae*: dependence on plasma membrane fatty acid composition". *Applied and Environmental Microbiology* 62.11 (1996): 3960-3966.

50. Shanmuganathan A., *et al*. "Copper-induced oxidative stress in *Saccharomyces cerevisiae* targets enzymes of the glycolytic pathway". *FEBS Letters* 556.1-3 (2004): 253-259.

51. Tucker CL and Fields S. "Quantitative genome-wide analysis of yeast deletion strain sensitivities to oxidative and chemical stress". *Comparative and Functional Genomics* 5.3 (2004): 216-224.

52. Huang ME., *et al*. "A genome wide screen in *Saccharomyces cerevisiae* for genes that suppress the accumulation of mutations". *Proceedings of the National Academy of Sciences of the United States of America* 100.20 (2003): 11529-11534.

53. Vallières C., *et al*. "Mitochondrial ferredoxin determines vulnerability of cells to copper excess". *Cell Chemical Biology* 24.10 (2017): 1228-1237.e3.

54. Islahudin F., *et al*. "The antimalarial drug quinine interferes with serotonin biosynthesis and action". *Scientific Reports* 4 (2014): 3618.

55. Avery SV and Tobin JM. "Mechanism of adsorption of hard and soft metal ions to *Saccharomyces cerevisiae* and influence of hard and soft anions". *Applied and Environmental Microbiology* 59.9 (1993): 2851-2856.

56. Smith MC., *et al*. "Glutathione and Gts1p drive beneficial variability in the cadmium resistances of individual yeast cells". *Molecular Microbiology* 66.3 (2007): 699-712.

57. Adamis PD., *et al*. "The effect of superoxide dismutase deficiency on cadmium stress". *Journal of Biochemical and Molecular Toxicology* 18.1 (2004): 12-17.

58. Sumner ER and Avery SV. "Phenotypic heterogeneity: differential stress resistance among individual cells of the yeast *Saccharomyces cerevisiae*". *Microbiology (Reading, England)* 148.2 (2002): 345-351.

59. Cerpa W., *et al*. "Is there a role for copper in neurodegenerative diseases?". *Molecular Aspects of Medicine* 26.4-5 (2005): 405-420.

60. Crow JP., *et al*. "Decreased zinc affinity of amyotrophic lateral sclerosis-associated superoxide dismutase mutants leads to enhanced catalysis of tyrosine nitration by peroxynitrite". *Journal of Neurochemistry* 69.5 (1997): 1936-1944.

61. Drakulic T., *et al*. "Involvement of oxidative stress response genes in redox homeostasis, the level of reactive oxygen species, and ageing in *Saccharomyces cerevisiae*". *FEMS Yeast Research* 5.12 (2005): 1215-1228.

62. Guidot DM., *et al*. "Mitochondrial respiration scavenges extramitochondrial superoxide anion via a nonenzymatic mechanism". *The Journal of Clinical Investigation* 96.2 (1995): 1131-1136.

63. Rodriguez JA., *et al*. "Destabilization of apoprotein is insufficient to explain Cu,Zn-superoxide dismutase-linked ALS pathogenesis". *Proceedings of the National Academy of Sciences of the United States of America* 102.30 (2005): 10516-10521.

64. Srinivasan C., *et al*. "Yeast lacking superoxide dismutase(s) show elevated levels of "free iron" as measured by whole cell electron paramagnetic resonance". *The Journal of Biological Chemistry* 275.38 (2000): 29187-29192.

65. Noor R., *et al*. "Superoxide dismutase--applications and relevance to human diseases". *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 8.9 (2002): RA210-RA215.

66. Koziol S., *et al*. "Antioxidants protect the yeast *Saccharomyces cerevisiae* against hypertonic stress". *Free Radical Research* 39.4 (2005): 365-371.

67. Chernyak BV., *et al*. "COVID-19 and oxidative stress". *Biochemistry* 85.12 (2020): 1543-1553.

68. Vollbracht C and Kraft K. "Oxidative stress and hyper-inflammation as major drivers of severe covid-19 and long covid: implications for the benefit of high-dose intravenous vitamin C". *Frontiers in Pharmacology* 13 (2022): 899198.

69. Martínez Leo EE., *et al*. "Ultra-processed diet, systemic oxidative stress, and breach of immunologic tolerance". *Nutrition (Burbank, Los Angeles County, Calif.)* 91-92 (2021): 111419.

70. Zhao H., *et al*. "Dynamic imaging of cellular pH and redox homeostasis with a genetically encoded dual-functional biosensor, pHaROS, in yeast". *The Journal of Biological Chemistry* 294.43 (2019): 15768-15780.

71. Reddi AR and Culotta VC. "SOD1 integrates signals from oxygen and glucose to repress respiration". *Cell* 152.1-2 (2013): 224-235.

72. Zyrina AN., *et al*. "Mitochondrial superoxide dismutase and Yap1p act as a signaling module contributing to ethanol tolerance of the yeast *Saccharomyces cerevisiae*". *Applied and Environmental Microbiology* 83.3 (2017): e02759-16.

73. Tsang EW., *et al*. "Differential regulation of superoxide dismutases in plants exposed to environmental stress". *The Plant Cell* 3.8 (1991): 783-792.

74. Dalleau S., *et al*. "Cell death and diseases related to oxidative stress: 4-hydroxynonenal (HNE) in the balance". *Cell Death and Differentiation* 20.12 (2013): 1615-1630.

75. Siperstein MD and Fagan VM. "Role of glycolysis in fatty acid and cholesterol synthesis in normal and diabetic rats". *Science (New York, N.Y.)* 126.3281 (1957): 1012-1013.

76. Spagnuolo MS., *et al*. "A short-term western diet impairs cholesterol homeostasis and key players of beta amyloid metabolism in brain of middle aged rats". *Molecular Nutrition and Food Research* 64.16 (2020): e2000541.

77. Fernández-Beltrán LC., *et al*. "A transcriptomic meta-analysis shows lipid metabolism dysregulation as an early pathological mechanism in the spinal cord of SOD1 mice". *International Journal of Molecular Sciences* 22.17 (2021): 9553.

78. Henning Y., *et al*. "Hypoxia aggravates ferroptosis in RPE cells by promoting the Fenton reaction". *Cell Death and Disease* 13.7 (2022): 662.

79. Tafuri F., *et al*. "SOD1 misplacing and mitochondrial dysfunction in amyotrophic lateral sclerosis pathogenesis". *Frontiers in Cellular Neuroscience* 9 (2015): 336.

80. Martins D and English AM. "SOD1 oxidation and formation of soluble aggregates in yeast: relevance to sporadic ALS development". *Redox Biology* 2 (2014): 632-639.

81. Brasil AA., *et al*. "The involvement of GSH in the activation of human Sod1 linked to FALS in chronologically aged yeast cells". *FEMS Yeast Research* 13.5 (2013): 433-440.

82. Wang Z., *et al*. "Secretion expression of SOD1 and its overlapping function with GSH in brewing yeast strain for better flavor and anti-aging ability". *Journal of Industrial Microbiology and Biotechnology* 41.9 (2014): 1415-1424.

83. Limone F., *et al*. "Single-nucleus sequencing reveals enriched expression of genetic risk factors in extratelencephalic neurons sensitive to degeneration in ALS". *Nature Aging* 4.7 (2024): 984-997.

84. Steinmeier J and Dringen R. "Exposure of cultured astrocytes to menadione triggers rapid radical formation, glutathione oxidation and Mrp1-mediated export of glutathione disulfide". *Neurochemical Research* 44.5 (2019): 1167-1181.

85. Yang F., *et al*. "Copper induces oxidative stress and apoptosis through mitochondria-mediated pathway in chicken hepatocytes". *Toxicology In Vitro* 54 (2019): 310-316.

86. Ursini F and Maiorino M. "Lipid peroxidation and ferroptosis: The role of GSH and GPx4". *Free Radical Biology and Medicine* 152 (2020): 175-185.

87. Tsang CK., *et al*. "Superoxide dismutase 1 acts as a nuclear transcription factor to regulate oxidative stress resistance". *Nature Communications* 5 (2014): 3446.

88. Crescenzo R., *et al*. "Effect of initial aging and high-fat/high-fructose diet on mitochondrial bioenergetics and oxidative status in rat brain". *Molecular Neurobiology* 56.11 (2019): 7651-7663.

89. Tan SX., *et al*. "Cu, Zn superoxide dismutase and NADP(H) homeostasis are required for tolerance of endoplasmic reticulum stress in *Saccharomyces cerevisiae*". *Molecular Biology of the Cell* 20.5 (2009): 1493-1508.

90. Richards MP., *et al*. "Effect of pH on structural changes in perch hemoglobin that can alter redox stability and heme affinity". *Journal of Aquatic Food Product Technology* 18.4 (2009): 416-423.

91. Burdette SC and Lippard SJ. "Meeting of the minds: metalloneurochemistry". *Proceedings of the National Academy of Sciences of the United States of America* 100.7 (2003): 3605-3610.

92. Mazzoli A., *et al*. "Early hepatic oxidative stress and mitochondrial changes following western diet in middle aged rats". *Nutrients* 11.11 (2019): 2670.

93. Hider R., *et al*. "The role of GSH in intracellular iron trafficking". *International Journal of Molecular Sciences* 22.3 (2021): 1278.

94. Circu ML and Aw TY. "Glutathione and apoptosis". *Free Radical Research* 42.8 (2008): 689-706.

95. Mollinedo F. "Lipid raft involvement in yeast cell growth and death". *Frontiers in Oncology* 2 (2012): 140.

96. Boggs SE., *et al*. "Glutathione levels determine apoptosis in macrophages". *Biochemical and Biophysical Research Communications* 247.2 (1998): 229-233.

97. Ghezzi P. "Role of glutathione in immunity and inflammation in the lung". *International Journal of General Medicine* 4 (2011): 105-113.

98. Okado-Matsumoto A and Fridovich I. "Subcellular distribution of superoxide dismutases (SOD) in rat liver: Cu,Zn-SOD in mitochondria". *The Journal of Biological Chemistry* 276.42 (2001): 38388-38393.

99. Leitch JM., *et al*. "Post-translational modification of Cu/Zn superoxide dismutase under anaerobic conditions". *Biochemistry* 51.2 (2012): 677-685.

100. Damiano S., *et al*. "Metabolism regulation and redox state: insight into the role of superoxide dismutase 1". *International Journal of Molecular Sciences* 21.18 (2020): 6606.

101. Maryon EB., *et al*. "Rate and regulation of copper transport by human copper transporter 1 (hCTR1)". *The Journal of Biological Chemistry* 288.25 (2013): 18035-18046.

102. Lee JA., *et al*. "Differential regulation of inducible nitric oxide synthase and cyclooxygenase-2 expression by superoxide dismutase in lipopolysaccharide stimulated RAW 264.7 cells". *Experimental and Molecular Medicine* 41.9 (2009): 629-637.

103. Allen RG., *et al*. "Expression and regulation of superoxide dismutase activity in human skin fibroblasts from donors of different ages". *Journal of Cellular Physiology* 165.3 (1995): 576-587.

104. Hernandez-Saavedra D., *et al*. "Redox regulation of the superoxide dismutases SOD3 and SOD2 in the pulmonary circulation". *Advances in Experimental Medicine and Biology* 967 (2017): 57-70.

105. Demchenko IT., *et al*. "Involvement of extracellular superoxide dismutase in regulating brain blood flow". *Neuroscience and Behavioral Physiology* 40.2 (2010): 173-178.

106. Pereira B., *et al*. "Hormonal regulation of superoxide dismutase, catalase, and glutathione peroxidase activities in rat macrophages". *Biochemical Pharmacology* 50.12 (1995): 2093-2098.

107. Hassan HM. "Biosynthesis and regulation of superoxide dismutases". *Free Radical Biology and Medicine* 5.5-6 (1988): 377-385.

108. Gort AS., *et al*. "The regulation and role of the periplasmic copper, zinc superoxide dismutase of *Escherichia coli*". *Molecular Microbiology* 32.1 (1999): 179-191.

109. Harris ED. "Copper as a cofactor and regulator of copper, zinc superoxide dismutase". *The Journal of Nutrition* 122.3 (1992): 636-640.

110. Itoh S., *et al*. "Novel mechanism for regulation of extracellular SOD transcription and activity by copper: role of antioxidant-1". *Free Radical Biology and Medicine* 46.1 (2009): 95-104.

111. Wang Y., *et al*. "Superoxide dismutases: Dual roles in controlling ROS damage and regulating ROS signaling". *The Journal of Cell Biology* 217.6 (2018): 1915-1928.

112. Miao L and St Clair DK. "Regulation of superoxide dismutase genes: implications in disease". *Free Radical Biology and Medicine* 47.4 (2009): 344-356.

113. Siperstein MD. "Glycolytic pathways; their relation to the synthesis of cholesterol and fatty acids". *Diabetes* 7.3 (1958): 181-188.

114. Wang BT., *et al*. "The mammalian target of rapamycin regulates cholesterol biosynthetic gene expression and exhibits a rapamycin-resistant transcriptional profile". *Proceedings of the National Academy of Sciences of the United States of America* 108.37 (2011): 15201-15206.

115. Van der Paal J., *et al*. "Hampering effect of cholesterol on the permeation of reactive oxygen species through phospholipids bilayer: possible explanation for plasma cancer selectivity". *Scientific Reports* 7 (2017): 39526.

116. Landis GN and Tower J. "Superoxide dismutase evolution and life span regulation". *Mechanisms of Ageing and Development* 126.3 (2005): 365-379.

117. Karavolos MH., *et al*. "Role and regulation of the superoxide dismutases of *Staphylococcus aureus*". *Microbiology (Reading, England)* 149.10 (2003): 2749-2758.

118. Ballal A and Manna AC. "Regulation of superoxide dismutase (sod) genes by SarA in *Staphylococcus aureus*". *Journal of Bacteriology* 191.10 (2009): 3301-3310.

119. Mishra P and Sharma P. "Superoxide dismutases (SODs) and their role in regulating abiotic stress induced oxidative stress in plants". In Reactive Oxygen, Nitrogen and Sulfur Species in Plants (eds M. Hasanuzzaman, V. Fotopoulos, K. Nahar and M. Fujita) (2019).

120. Alscher RG., *et al*. "Role of superoxide dismutases (SODs) in controlling oxidative stress in plants". *Journal of Experimental Botany* 53.372 (2002): 1331-1341.

121. Mishra N., *et al*. "Achieving abiotic stress tolerance in plants through antioxidative defense mechanisms". *Frontiers in Plant Science* 14 (2023): 1110622.

122. Wang W., *et al*. "Gene expression characteristics and regulation mechanisms of superoxide dismutase and its physiological roles in plants under stress". *Biochemistry* 81.5 (2016): 465-480.

123. Van Camp W., *et al*. "The regulation and function of tobacco superoxide dismutases". *Free Radical Biology and Medicine* 23.3 (1997): 515-520.

124. Feng YC., *et al*. "Regulation of three isoforms of SOD gene by environmental stresses in citrus red mite, *Panonychus citri*". *Experimental and Applied Acarology* 67.1 (2015): 49-63.

125. Ai H., *et al*. "Regulation of three subtypes of SOD gene in *Aleuroglyphus ovatus* (Acari: Acaridae) under lead stress". *Archives of Insect Biochemistry and Physiology* 114.3 (2023): e22043.

126. Abrego-Guandique DM., *et al*. "β-carotene impacts the liver microRNA profile in a sex-specific manner in mouse offspring of western diet-fed mothers: results from microarray analysis by direct hybridization". *International Journal of Molecular Sciences* 25.23 (2024): 12899.

127. Ammendolia DA., *et al*. "Plasma membrane integrity: implications for health and disease". *BMC Biology* 19.1 (2021): 71.

128. Togo T. "Signaling pathways involved in adaptive responses to cell membrane disruption". *Current Topics in Membranes* 84 (2019): 99-127.

129. Muller MP., *et al*. "Characterization of lipid-protein interactions and lipid-mediated modulation of membrane protein function through molecular simulation". *Chemical Reviews* 119.9 (2019): 6086-6161.

130. Shea R., *et al*. "Magnification of cholesterol-induced membrane resistance on the tissue level: implications for hypoxia". *Advances in Experimental Medicine and Biology* 923 (2016): 43-50.

131. Olżyńska A., *et al*. "Tail-oxidized cholesterol enhances membrane permeability for small solutes". *Langmuir* 36.35 (2020): 10438-10447.

132. Demel RA., *et al*. "The effect of sterol structure on the permeability of lipomes to glucose, glycerol and Rb +". *Biochimica et Biophysica Acta* 255.1 (1972): 321-330.

133. Ayala A., *et al*. "Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal". *Oxidative Medicine and Cellular Longevity* (2014): 360438.

134. Gaschler MM and Stockwell BR. "Lipid peroxidation in cell death". *Biochemical and Biophysical Research Communications* 482.3 (2017): 419-425.

135. Dif N., *et al*. "Insulin activates human sterol-regulatory-element-binding protein-1c (SREBP-1c) promoter through SRE motifs". *The Biochemical Journal* 400.1 (2006): 179-188.

136. Sekiya M., *et al*. "Oxidative stress induced lipid accumulation via SREBP1c activation in HepG2 cells". *Biochemical and Biophysical Research Communications* 375.4 (2008): 602-607.

137. Léger-Charnay E., *et al*. "Is 24(S)-hydroxycholesterol a potent modulator of cholesterol metabolism in Müller cells? An *in vitro* study about neuron to glia communication in the retina". *Experimental Eye Research* 189 (2019): 107857.

138. Fukai T and Ushio-Fukai M. "Superoxide dismutases: role in redox signaling, vascular function, and diseases". *Antioxidants and Redox Signaling* 15.6 (2011): 1583-1606.

139. Brand MD. "Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling". *Free Radical Biology and Medicine* 100 (2016): 14-31.

140. Adesina SE., *et al*. "Targeting mitochondrial reactive oxygen species to modulate hypoxia-induced pulmonary hypertension". *Free Radical Biology and Medicine* 87 (2015): 36-47.

141. Peggion C., *et al*. "SOD1 in ALS: Taking stock in pathogenic mechanisms and the role of glial and muscle cells". *Antioxidants (Basel, Switzerland)* 11.4 (2022): 614.

142. Petrov AM., *et al*. "Brain cholesterol metabolism and its defects: linkage to neurodegenerative diseases and synaptic dysfunction". *Acta Naturae* 8.1 (2016): 58-73.

143. Ayciriex S., *et al*. "Neuronal cholesterol accumulation induced by Cyp46a1 down-regulation in mouse hippocampus disrupts brain lipid homeostasis". *Frontiers in Molecular Neuroscience* 10 (2017): 211.

144. Koga M., *et al*. "Glutathione is a physiologic reservoir of neuronal glutamate". *Biochemical and Biophysical Research Communications* 409.4 (2011): 596-602.

145. Sedlak TW., *et al*. "The glutathione cycle shapes synaptic glutamate activity". *Proceedings of the National Academy of Sciences of the United States of America* 116.7 (2019): 2701-2706.

146. Yaribeygi H., *et al*. "Molecular mechanisms linking oxidative stress and diabetes mellitus". *Oxidative Medicine and Cellular Longevity* (2020): 8609213.

147. Galaris D., *et al*. "Iron homeostasis and oxidative stress: An intimate relationship". *Biochimica et Biophysica Acta. Molecular Cell Research* 1866.12 (2019): 118535.

148. Ruiz LM., *et al*. "Role of copper on mitochondrial function and metabolism". *Frontiers in Molecular Biosciences* 8 (2021): 711227.

149. Uriu-Adams JY and Keen CL. "Copper, oxidative stress, and human health". *Molecular Aspects of Medicine* 26.4-5 (2005): 268-298.

150. Kazi TG., *et al*. "Interaction of copper with iron, iodine, and thyroid hormone status in goitrous patients". *Biological Trace Element Research* 134.3 (2010): 265-279.

151. Saito T. "Superoxide dismutase level in human erythrocytes and its clinical application to the patients with cancers and thyroidal dysfunctions". *[Hokkaido Igaku Zasshi] The Hokkaido Journal of Medical Science* 62.2 (1987): 257-268.

152. Kim MJ., *et al*. "Exploring the role of copper and selenium in the maintenance of normal thyroid function among healthy Koreans". *Journal of Trace Elements in Medicine and Biology* 61 (2020): 126558.

153. Boyd SD., *et al*. "Copper sources for Sod1 activation". *Antioxidants (Basel, Switzerland)* 9.6 (2020): 500.

154. Chen JJ and Yu BP. "Alterations in mitochondrial membrane fluidity by lipid peroxidation products". *Free Radical Biology and Medicine* 17.5 (1994): 411-418.

155. Mannarino SC., *et al*. "Requirement of glutathione for Sod1 activation during lifespan extension". *Yeast (Chichester, England)* 28.1 (2011): 19-25.

156. Neumann EN., *et al*. "Brainwide silencing of prion protein by AAV-mediated delivery of an engineered compact epigenetic editor". *Science (New York, N.Y.)* 384.6703 (2024): ado7082.

157. Huang TT., *et al*. "Oxidative stress and redox regulation on hippocampal-dependent cognitive functions". *Archives of Biochemistry and Biophysics* 576 (2015): 2-7.

158. Rye MB., *et al*. "Cholesterol synthesis pathway genes in prostate cancer are transcriptionally downregulated when tissue confounding is minimized". *BMC Cancer* 18.1 (2018): 478.

159. Horn A and Jaiswal JK. "Structural and signaling role of lipids in plasma membrane repair". *Current Topics in Membranes* 84 (2019): 67-98.

160. Mason RP. "Molecular mechanisms underlying the effects of cholesterol on neuronal cell membrane function and drug-membrane interactions". In M. Hillbrand and R. T. Spitz (Eds.: Lipids, health, and behavior) American Psychological Association (1997): 127-138.

161. Morgan AE., *et al*. "Cholesterol metabolism: A review of how ageing disrupts the biological mechanisms responsible for its regulation". *Ageing Research Reviews* 27 (2016): 108-124.

162. Luo J., *et al*. "Mechanisms and regulation of cholesterol homeostasis". *Nature Reviews. Molecular Cell Biology* 21.4 (2020): 225-245.

163. Bakadia BM., *et al*. "The impact of oxidative stress damage induced by the environmental stressors on COVID-19". *Life Sciences* 264 (2021): 118653.

164. Reiken S., *et al*. "Alzheimer's-like signaling in brains of COVID-19 patients". *Alzheimer's and Dementia* 18.5 (2022): 955-965.

165. Riondel P., *et al*. "Evidence for two subpopulations of cerebrospinal fluid-contacting neurons with opposite GABAergic signaling in adult mouse spinal cord". *The Journal of Neuroscience* 44.22 (2024): e2289222024.

166. Dowling DK and Wolff JN. "Evolutionary genetics of the mitochondrial genome: insights from *Drosophila*". *Genetics* 224.3 (2023): iyad036.

167. Kuo LC., *et al*. "Infection of *Mycoplasma hominis* in the left lower leg amputation wound of a patient with diabetes: a case report". *Journal of Medical Case Reports* 18 (2024): 380.

168. Ristic-Medic D., *et al*. "Liver disease and COVID-19: The link with oxidative stress, antioxidants and nutrition". *World Journal of Gastroenterology* 27.34 (2021): 5682-5699.

169. Brugge K., *et al*. "Correlations of glutathione peroxidase activity with memory impairment in adults with Down syndrome". *Biological Psychiatry* 46.12 (1999): 1682-1689.

170. Hackler J., *et al*. "Relation of serum copper status to survival in COVID-19". *Nutrients* 13.6 (2021): 1898.

171. Raha S., *et al*. "Is copper beneficial for COVID-19 patients?". *Medical Hypotheses* 142 (2020): 109814.

172. Francis Z., *et al*. "The COVID-19 pandemic and zinc-induced copper deficiency: an important link". *The American Journal of Medicine* 135.8 (2022): e290-e291.

173. Rock E., *et al*. "The effect of copper supplementation on red blood cell oxidizability and plasma antioxidants in middle-aged healthy volunteers". *Free Radical Biology and Medicine* 28.3 (2000): 324-329.

174. Ram-Mohan N., *et al*. "SARS-CoV-2 RNAemia predicts clinical deterioration and extrapulmonary complications from COVID-19". *Clinical Infectious Diseases* 74.2 (2022): 218-226.

175. Khouri R., *et al*. "SOD1 plasma level as a biomarker for therapeutic failure in cutaneous leishmaniasis". *The Journal of Infectious Diseases* 210.2 (2014): 306-310.

176. Hwang J., *et al*. "SOD1 suppresses pro-inflammatory immune responses by protecting against oxidative stress in colitis". *Redox Biology* 37 (2020): 101760.

177. Madi M., *et al*. "Status of serum and salivary levels of superoxide dismutase in type 2 diabetes mellitus with oral manifestations: a case control study". *Ethiopian Journal of Health Sciences* 26.6 (2016): 523-532.

178. Muscogiuri G., *et al*. "Genetic disruption of SOD1 gene causes glucose intolerance and impairs β-cell function". *Diabetes* 62.12 (2013): 4201-4207.

179. Paolisso G., *et al*. "Plasma GSH/GSSG affects glucose homeostasis in healthy subjects and non-insulin-dependent diabetics". *The American Journal of Physiology* 263.3.1 (1992): E435-E440.

180. Barbagallo M., *et al*. "Cellular ionic alterations with age: relation to hypertension and diabetes". *Journal of the American Geriatrics Society* 48.9 (2000): 1111-1116.

181. Barbagallo M., *et al*. "Effects of vitamin E and glutathione on glucose metabolism: role of magnesium". *Hypertension (Dallas, Tex.) 1979* 34.4.2 (1999): 1002-1006.

182. Buh A., *et al*. "Impact of electrolyte abnormalities and adverse outcomes in persons with eating disorders: A systematic review protocol". *PloS one* 19.8 (2024): e0308000.

183. Glover G., *et al*. "Nutrient and salt depletion synergistically boosts glucose metabolism in individual *Escherichia coli* cells". *Communications Biology* 5.1 (2022): 385.

184. Lee HB., *et al*. "*Aspergillus ullungdoensis sp. nov., Penicillium jeongsukae sp. nov.,* and other fungi from Korea". *Fungal Biology* 128.8B (2024): 2479-2492.

185. Xu M., *et al*. "Exploiting phenotypic heterogeneity to improve production of glutathione by yeast". *Microbial Cell Factories* 23.1 (2024): 267.

186. Rab FA. "Role of food-its influence on modulation of therapies including chemotherapy's outcomes". *EC Nutrition* 20.2 (2025): 01-31.

187. Adamis PD., *et al*. "The role of glutathione transferases in cadmium stress". *Toxicology Letters* 154.1-2 (2004): 81-88.

188. Montanari M., *et al*. "Autism spectrum disorder: focus on glutamatergic neurotransmission". *International Journal of Molecular Sciences* 23.7 (2022): 3861.

189. Deuel RK. "Autism: a cognitive developmental riddle". *Pediatric Neurology* 26.5 (2002): 349-357.

190. Maenner MJ., *et al*. "Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 Sites, United States, 2020". *Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.) 2002* 72.2 (2023): 1-14.

Volume 21 Issue 2 February 2026