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Review Article

Role of Food-Its Influence on Modulation of Therapies Including Chemotherapy's Outcomes

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Abstract

Food provides basic ingredients that a given living body can or cannot synthesis to enable it to perform its normal functions, in addition to providing energy. Another under-acknowledged role of food is to protect the given body from illness and to cure current ailment on regular use. Many non-contagious diseases share the same interconnected genomic or epigenetically driven molecular pathways leading to cause illnesses as well as to decide the fate of illnesses and associated complications whereas food plays a critical role in deciding the extent of severity and the fate of illnesses and its associated complications mainly by effecting oxidative stress shifts in the body modulating genes networks operations' regulation involving genomic and/or involving epigenetic driven pathways by effecting homeostasis. The effect of the therapies can be modulated by type of processed or un-processed food intake. This piece of work reveals the missing understanding in the treatment strategies that are being used to treat most of the non-contagious diseases, including cancer. For this reason, patients are being dying not of diseases but due to inappropriate approach of therapies and food recommendations and complications associated with the therapies and their management. This paper also provides some understanding on current cancer therapy strategies responsible for intensifying the cancer illness and its associated consequences.

This paper is based on current understanding of knowledge, revealing the underlying molecular mechanisms responsible for causing illnesses as well as for deciding fate of illnesses and associated complications sharing the same interconnected genomics and/or involving epigenetic driven molecular pathways in addition to discussing some appropriate universal food combination models' features constituting the food therapy that can be helpful to modulate the outcome of other therapies particularly cancer therapies leading to complete cure.

Keywords: *Food; Modulation of Therapies; Chemotherapy; Genes Networks Operations' Regulation; Non-Contagious Diseases; Food Therapy; Desi Food; Epigenetics; Universal Evolutionary Capacitor; Consumers' Safety; Natural Health; Stress Chemistry; Knowledge Gap*

Introduction

Food

Anything solid or liquid that is not the integral part of a given living entity and that a living body intakes either to get energy and to get other bioactive ingredients or for both the purposes is called food [1]. In addition to this food has its scientifically proven role in protecting the human body from illnesses and in modulating the course of illnesses and associated complications leading to complete cure on regular use [2-6].

Role of food in modulating genomic and epigenetic molecular pathways

Human beings are composed of a vast number of cells, subsets of which co-ordinate to form tissues. These tissues constitute organs, which perform specialized functions. Together, these organs form biological systems that drive the body's normal physiological operations [7]. The regulatory information governing cell functions, structural makeup, and expression of specific phenotypes (observable characteristics under given conditions) is stored in sequences of coded nucleotides. Each code is made up of a sequence of three nitrogenous bases, integral parts of nucleotides. These nucleotides serve as the building blocks of DNA polymers. Other than a few codons, which code for initiation or termination of protein synthesis, each three-base sequence (codon) codes for a specific amino acid, forming the reading frame of a gene.

The DNA polymer forms a double helix through base pairing with complementary strands, which replicates to transfer genetic material to progeny cells. According to classical biology, any change in the sequence of codes (codons) within a gene's reading frame is termed a mutation, which can abort a given biological function, alter it or have no effect. The hereditary information, encoded in the gene's reading frame, undergoes transcription to form RNA, which is then translated into polypeptides-such as enzymes and other cell components [8].

According to the findings reported over two decades ago, these enzymes catalyze the ongoing biochemical reactions including synthesis and degradation of cell components, regulation of cellular functions, ongoing evolutionary events of cell, conservation and transfer of genetic material to progeny cells and ultimately decide the cells' fate which in turn are also inter-dependently co-regulated by genes operations' networks at transcriptional level [9,10]. This has raised serious doubts on understanding of findings which indicate the existence of co-relations among defeats in proteins, cells survival and illness causing potentials [11]. It has been demonstrated by using yeast model which has considerable homology with human genome and is a widely used tool for studying genes' functions [12-14] that the physical, chemical and/or biochemical stimuli or biological events can alter the effects of mutations that impair the function of essential genes operating within the same genes operations' regulatory network and are co-regulated at transcriptional level by feedback mechanism which in turn, is also regulated by iron-copper associated and dissociated ionic equilibrium balance shifts driving the oxidative stress shifts or alter homeostasis within cells and across the physiological systems in the living body [9,10,15-18]. This process can enhance the functions of weaker genes. As an outcome, under stress condition such as oxidative stress shifts can affect both the physiology of cells and ongoing biochemical processes that are being modulated differently at genes operations' networks at regulatory level, ultimately altering the cells' fate. These changes drive the cells to resume environmentally well adopted cellular phenotypes by epigenetically driven molecular pathways (change in genes expression within a given genes operations' regulatory network or networks without any change in DNA sequences (codons) of the reading frames) thereby limiting the effects of mutations. This adoptive process, one of the underlying process that enables healthy cells to evolve as an altered cellular phenotypes and to escape apoptosis and other cells' pre-death events, also influences cell growth, repairing and aging processes while conferring on healthy progeny cells augmented potential to evade a wider range of pre-death events such as apoptosis, necrosis, ferroptosis modulated by differently operating genes networks co-regulated by Universal Evolutionary Capacitor's Gene- and its products-*SOD1*-Sod1p (*SOD1* encodes for superoxide dismutase (sod1p) a copper/zinc-binding enzyme) driving the evolution of progeny cellular phenotypes better suited to the altered environment within or outside the cells

in the body [9,10,15-30]. Under extreme stress conditions, the living entities normal molecular pathways, genetically programmed innate roles of enzymes' molecules, structural molecules, precursors, intermediate products, by-products and end products transform to acquire altered roles and characteristics revealing the knowledge of newly evolved understanding of stress chemistry. For instance, superoxide dismutase (sod1p) has antioxidant role under aerobic conditions in presence of ample sustainable copper supply but in presence of carbon dioxide under hypoxia superoxide dismutase (sod1p) behaves as peroxidase, facilitating biochemical reactions without release of copper ions from superoxide dismutase (sod1p) molecules unlike when it acts in its dismutase enzymatic role, catalyzing the biochemical reactions with release of copper ions [10,31-33].

These findings confirm the prophylactic and therapeutic role of food, key player to effect the homeostasis driven oxidative stress shifts modulating the genes networks operations' regulation, also in the cases, where health manifestations can be linked with mutations and/or in any other health shortcomings especially in children whose most of the illnesses can be suppressed or be cured if pure natural diet, is regularly consumed while avoiding hyper-processed commercially prepared food, the key player to cause heightened oxidative stress driven shift in homeostasis in the body, adversely effecting the growth of children and their current health.

One of the most novel findings of prevailing era

Basic understanding

As it is mentioned earlier that a physical chemical or biochemical stimuli or biological events including injury can alter the impact of mutations causing the loss of functions of certain essential genes operational within the same genes network regulated at transcriptional level by boosting up the activity of comparatively weaker genes whereas, *SOD1*, which encodes for superoxide dismutase (sod1p) that with bounded copper and zinc ions in its structure, destroys the free superoxide radicals, reactive form of oxygen, including those radicals leaking from electron transport chain (respiratory chain) and *CTR1*, which encodes for copper transporter 1 (Ctr1p) a plasma protein that acts as a high affinity membrane copper transporter, (both genes) are connected through the same genes-operation-regulatory-pathway and are co-regulated reciprocally (by feedback mechanism) at transcriptional level in copper concentration gradient dependent manner [4,5,9,10,15,16,34-41] which is modulated by copper and iron associated and dissociated ionic equilibrium balance driving oxidative stress shifts, disturbing homeostasis with or without change in pH.

On depriving dismutase activity possessed by superoxide dismutase (sod1p), superoxide radicals can strip electrons from cellular molecules essential for proper cell functions besides causing electrostatic turbulence, oxidative stress and pH shift [25,33,36]. It is evident that oxidative stress modulates the interconnection that exists among the diverse genes networks epigenetically regulated at the level beyond the functions encoded by individual genes, being effected by any alteration in the basic functional unit of genome such as gene as an outcome impact or impacts of mutation or mutations are confined to a limit or vanish completely, switching target cells programmed involving the given genes operations regulatory networks for cell death or appearance of damaged cells (necrosis) in certain situations to evolving cellular systems with better adoption with and/or without impairment in the cells depending upon the target cells, their environment, repairing processes in action and adaption inducing stimuli [4,5,9,10,15,16,34-46] a common manifestation of many non-infectious diseases including mental illnesses, dementia etc. whereas prolonged progression of damaged cells (injury) can finish cell to cell contact inhibition or can result in diminishing the cell-to–cell-contact-inhibition phenomena as an outcome of losing the control of modulation of regulatory pathways based on cellular environment sensed at genetic level coupled with altered cell membrane permeability within a given cells populations in target tissues, creating pockets of patches comprised of variant cells (adapted impaired cells) with having deprived access to detoxifying nutrients otherwise rich in lethal components such as oxidative stress inducing agents and cellular debris leading to gradual transformation driven evolution of multiclonal tumors [4,5,9,10,15,16,34-47] or plagues formation depending on the type of cells involved and their environment, as it happens in Alzheimer, for having the genes regulatory operations'

networks targeted differently as cells involved are in different generation numbers and in different stages of cell cycle for being replicated at different rates. These cells escape death by nullifying the effects of pre-death events inducing stimuli [46,48-50].

Since in response of biological events or triggering biochemical, chemical, physical stimuli or as a result of an injury, genes operations' regulatory networks are targeted differently as an outcome driving variable shifts in oxidative stress; certain stressors are proven more lethal at lower concentration whereas their toxicity diminishes as their concentrations are increased, a very unusual phenomena reported by Rab in 2007 [10].

Inflammation is an intermediate manifestation of cells injury at tissue level and plays a significant role in limiting the impact of cellular manifestations particularly those happen as an outcome of oxidative stress shifts and in response of spreading infectious agents including viruses and immunogens etc. [45,51,52]. In parallel to fluctuating oxidative stress, repairing processes are launched which are regulated epigenetically involving superoxide dismutase (sod1p), glutathione (GSH), iron ions, copper ions, in addition to cellular cholesterol bio-synthesis levels and cellular carbohydrate metabolism modes and levels by the underlying molecular processes driving their inter-related dynamics to be discussed in upcoming publications.

Translation of novel findings in food systems-Multiple diseases prophylactics and food therapy

Most of the food ingredients are naturally obtained from biological origin when domestically processed at small scale (freshly prepared) or are processed by natural fermentation are rich in superoxide dismutase (sod1p), glutathione (GSH), iron ions, copper ions, chelating agents from biological origin, many of them have potential to carry ligands across the cells to the target sites in un-interrupted manner. Many of these biologically significant biochemical species can pass blood brain barrier without altering their native structure and characteristics. High level of free iron can drive ferroptosis, a form of epigenetically regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides at lethal levels. Chelating agents from biological origin present in the food on one hand chelates the free iron and/or other minerals available in the cells and across them in the body whereas on other hand support the un-interrupted supply of copper and other minerals to the cells including the target molecules where they canact as co-factor such as copper is for superoxide dismutase (sod1p), a key molecule for facilitating healing process and for limiting cellular injury in addition to buffering oxidative stress simultaneously.

Food therapy strategy is different from medicinal concept of therapy and from natural or herbal medicine therapy as it involves multiple and diversified food systems based solutions, suspensions, mixtures, complexes derived from biological origin, in addition to micro-structures trapping microbes, composing food preparations, many are present on the food surfaces as well. Food used for food therapy is generally processed at domestic level at a small scale (freshly prepared) while conserving the bioactive chemical and biochemical entities and their carriers to facilitate their un-interrupted transport to the active sites, a few critical features of food therapy which are deficient in classical medicine practice and natural or herbal medicine practice.

Desi Food (food originated from Pakistan, Bangladesh and India) represents a classical model of food systems having desirable features required to be used for food therapy. It is worth mentioning that in ancient days many desi foods were designed by the health experts by using locally available food ingredients, prepared domestically by using minimal processing exhibiting prophylactic and therapeutic roles on regular consumption [3].

Basic nutrition

Food provides nourishment in addition to providing energy, bioactive chemical and biochemical entities, and probiotics. Metabolic batteries operating in human body have potential to inter-convert protein, fat and carbohydrate, in addition to synthesizing other precursors, products and by-products in the living systems. Essential nutrients e.g. essential amino acids, essential fatty acids, vitamins

etc. are those bioactive chemicals which human body needs for performing normal functions but cannot synthesize them, so must be taken in food [53].

Sugar and its relation with oxidative stress

Glucose provides energy and nicotinamide adenine dinucleotide (NAD) + hydrogen/1,4- dihydronicotinamide adenine dinucleotide (NAD+/NADH) by undergoing process of glycolysis generating pyruvate. In presence of free oxygen (aerobic respiration), pyruvate is broken down in carbon dioxide and water by multi-stage reactions catalyzed by superoxide dismutase (sod1p) and by catalase enzyme which are involved to break down superoxide (O_2^-) and/or hydrogen peroxide (H_2O_2) respectively formed in response of leaked electrons to be delivered to oxygen to produce superoxide (O_2^-) and/or hydrogen peroxide (H_2O_2) while releasing more adenosine triphosphate (ATPs) and recycling 1,4- dihydronicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD) besides supporting other undergoing associated biochemical reactions [31,32,54].

In scarcity or absence of free oxygen with having heightened energy demand, pyruvate molecules break down into lactic acid while generating energy and recycling 1,4-dihydronicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD) by undergoing lactic acid fermentation.

In case, when there is insufficient supply of copper ions to superoxide dismutase (sod1p) to confer enzymatic activity on the molecules, scarcity of free oxygen and/or in response of higher levels of available glucose due to insulin deficiency and/or insulin tolerance altogether in response of any of these conditions can induce glycemic shifts associated with heightened oxidative stress, leading to formation of plague like structures composed of cell debris in vessels and organs, escaping death process initiation in response of increased cell-to-cell variability, one of the consequences of hemoglobin molecules driven oxidation particularly in cell membranes' cholesterol structure on release of free iron in response of heightened oxidative stress [55-59].

Insufficient supply of copper ions to superoxide dismutase (sod1p) or low oxygen levels inhibits dismutase enzymatic activity possessed by superoxide dismutase (sod1p) molecules, scarcity of free oxygen alone independent to sugar levels are sufficient to increase oxidative stress in the cells by virtue of superoxide dismutase (sod1p) molecules' peroxidase activity acquired in presence of carbon dioxide (CO_2) and across them, disturbing homeostasis leading to formation of plague like structures composed of cell debris in vessels and organs, escaping death events in response of increased cell-to-cell variability, as already mentioned earlier, is one of the consequences of hemoglobin molecules driven oxidation particularly in cell membranes' cholesterol structure on release of free iron in response of heightened oxidative stress [10,31-33,55-62].

Fructose has comparatively lower glycemic index than glucose in addition to this, fructose can enter in target cells in insulin independent manner unlike glucose [63-71].

Illness, therapy-oxidative stress, nutritional and bio-energetic crisis

As it has been mentioned earlier that physical, chemical and/or biochemical stimuli or biological events can alter the effects of mutations that impair the functions of essential genes operating within same genes regulatory network and are co-regulated at transcriptional level by feedback mechanism which in turn, is also regulated by iron-copper associated and dissociated ionic equilibrium balance shifts driving the oxidative stress to alter homeostasis within cells and across physiological systems in the living body, demonstrated as fluctuation in oxidative stress, pH and by further disturbing homeostasis which in addition to deciding fate of cells, can alter associated innate healing/repair pathways, conferring on the cellular components, chemical entities and biochemical compounds new roles with altered characteristics [4,5,9,10,15,16,33-46].

These physical, chemical and biochemical stimuli or biological events can occur as a consequence of illness or its molecular target therapy, immunotherapy or chemotherapy, boosting oxidative stress alone or associated with shifts in pH and disturbing homeostasis altogether creating nutritional and bio-energetic crisis, putting survival and growth of healthy cells at stake while putting repairing and regenerating cellular pathways at halt with or without effecting the targeted cancerous cells [72-77].

In order to combat heightened oxidative stress and to support repairing phenomena which is regulated epigenetically involving key players such as superoxide dismutase (sod1p), glutathione (GSH), iron ions, copper ions in addition to cellular cholesterol bio-synthesis levels and carbohydrate metabolism modes and levels at cellular level, food therapy strategy based on sustainable supply of superoxide dismutase (sod1p), glutathione (GSH) and copper ions to body in addition to supporting cellular cholesterol bio-synthesis levels and shifting from insulin-dependent-sugars such as glucose (require insulin for entry in target cells) to insulin-independent-sugars such as fructose (do not require insulin to enter in target cells) can be provided by intake of food items such as fresh natural food, vegetables, fruits, brown sugar (guur), natural (organic) un-pasteurized honey, naturally fermented food such as yogurt, cheese, pickles, minimally boiled egg, ghee extracted by churning butter, butter, water containing-fresh lemon juice with added Himalayan salt and brown sugar (guur), and domestically prepared desi food by using fresh natural ingredients and by following authentic recipes with needed modification as per consumer 's individual requirements [3].

It is important to avoid all food items that support in building free iron pools in cells and across them in the body in order to support natural healing process and to boost the survival of healthy and environmentally well-adopted cellular phenotypes particularly in those patients who are on therapies such as cancer therapy. Prefer halal or kosher meat, grass fed chicken with skin over other types of meat, added in desi food containing naturally fermented yogurt, fenugreek seeds, dried fenugreek leaves, nutmeg, mace, bishops weed, during cooking with fresh or dried spices and herbs free from preservatives. Eat raw vegetables with peel particularly the coloured ones. Prefer eating mixed fruits e.g. mango, plum (with peel), apricot (with peel), grapes (with peel), banana, watermelon, cantaloupe, unripe dates (with peel), unripe almond (with peel) apple (with peel) Grewia asiatica, strawberry, black plum cut into small pieces. Drink fresh juices having respective fruit fibers after adding brown sugar (guur), Himalayan salt and black paper powder. Eating mixture of fruits with peel cut into small pieces prevents sudden glycemic index shift unlike it happens on consuming high sugar levels containing food. Drink water with added fresh lemon juice, Himalayan salt and brown sugar (guur). To cope with nutrition and digestion crisis give freshly prepared digestion friendly preparation made by adding 2 teaspoon full sago or tapioca pearls in 200 ml water. Boil the mixture with continuous stirring until it becomes viscous. Add milk and further boil it for 3- 6 minutes at low flame. Leave the preparation for 45 minutes at room temperature. Add ½ to 1 teaspoon full natural (organic) un-pasteurized honey in the preparation before giving it to patients [3,4].

Naturally fermented food items intake, boosts healing processes while playing significant role in combating oxidative stress shifts and fluctuation in homeostasis indirectly as well as directly involving the gut physiology [3-6,78-85].

Avoid food having ingredients other than natural and biologically originated ones. It includes hyper-processed commercially manufactured food items particularly those food items which have extended shelf lifes conferred by adding preservatives as well as those food items having ingredients which have been stored for a very long time. Illness and its therapy both cause boost in oxidative stress [72-77,86,87] associated with or without injury. In order to boost repairing processes, sustainable intake of diverse varieties of food items enriched in nutrients and bioactive compounds originated from natural and biological sources is needed, recommending no dietary restrictions other than consuming hyper-processed commercially prepared food items or food items having preservatives and/or prolonged stored food items or food items designed for prolonged storage other than by using dying and/or freezing as preservation techniques.

Cancer molecular interplay and food therapy

Cancer is defined as a disease in which cells undergo un-controlled growth superseding the number of healthy cells while confining their activity and functions and can spread in rest of the body by penetrating in other tissues and organs [88-90].

Classical hypothesis about cancer and its relation with mutations and shift in genes networks operations' regulation, preliminary governed by inherited or somatic alteration in genes has changed since the reported findings by Rab in 2007 over twenty years ago which are yet unpublished [9,10,91,92].

Cancer cells exhibit heightened oxidative stress levels, hypoxia, altered pH, high energy demand, uncontrolled growth, a more acidic extra-cellular environment and a slightly alkaline intra-cellular environment, high levels of copper and iron pools, superoxide dismutase (sod1p), glutathione (GSH), normal to higher cellular cholesterol bio-synthesis levels with acquiring the potentials to use insulin-dependent-sugars such as glucose (require insulin for entry in target cells) and insulin-independent-sugars such as fructose (do not require insulin for entry in target cells) to fulfill the additional and diverse requirements of energy, nutrients and structural and functional precursors [86,87,93-97].

Wrong food and current cancer therapies favor cancer cells survival at the cost of healthy cells

It has been mentioned earlier that a physical, chemical or biochemical stimuli or biological event can alter effect or effects of mutation or mutations causing loss of functions of certain essential genes operational within the same genes network regulated at transcriptional level by boosting up activity of comparatively weaker genes whereas, *SOD1,* which encodes for superoxide dismutase (sod1p) that with bounded copper and zinc ions in its structure, destroys free superoxide radicals, reactive form of oxygen, including those radicals leaking from electron transport chain (respiratory chain) and *CTR1,* which encodes for copper transporter 1 (Ctr1p) a plasma protein that acts as a high affinity membrane copper transporter, (the both genes) lie within the same genes operation regulatory network and are co-regulated reciprocally (by feedback mechanism) at transcriptional level in copper concentration gradient dependent manner [4,5,9,10,15,16,34-41] which is modulated by copper and iron associated and dissociated ionic equilibrium balance driving oxidative stress shifts, distorting homeostasis with or without any change in pH.

This understanding on knowledge has conferred additional roles on minerals and other key molecules particularly on superoxide dismutase (sod1p), glutathione (GSH), iron, copper, on cellular cholesterol bio-synthesis levels and on chelating agents and transporter peptides depending on intra-cellular and extra-cellular conditions and on their environment, on their forms and on sustainable availability within cells and across them. Food therapy can provide all these ingredients and facilitate their sustainable conserved absorption and transportation to targeted sites in minimal time in safe and cost effective manner.

As already mentioned earlier that oxidative stress is heightened in cancer cells [87,95] and at the same time, cancer cells are generally more susceptible to oxidative stress proposing oxidative-stress-therapy based on selective cancer cells exposure to oxidizing agents, a possible means to treat cancer leading to complete cure [96,97]. But in reality strategy of cancer treatment based on boosting oxidative stress hinders the repairing processes as exposing healthy cells to high oxidative stress inhibits their growth and put them in nutritional and energy crisis whereas cancerous cells under the same conditions have benefit to compete for nutrition, energy, space with healthy cells by virtue of their higher rate of growth, by their ability to utilize glucose and fructose as source of energy and nutrition, by occupying more space and by dispersing in larger area in a given time than the same number of healthy cells. For this reason, in most of the cases, it is a wrong strategy of cancer treatment and wrong food recommendations which are more responsible for cancer-treatment-associated-complications leading to occurrence of death than the cancer disease progression itself particularly in the cases where patients are not consuming desi diet.

Cancer-oxygen nutrition cell integrity space and *SOD1*-Sod1p inter-dependent dynamics

With superseding growth of cancer cells, there arises a competition for oxygen, energy, nutrition and space between the cancer cells and healthy cells. Cancer cells acquire potentials to metabolize insulin-independent-sugars such as fructose (do not require insulin for entry in target cells) in addition to insulin-dependent-sugars such as glucose (require insulin for entry in target cells) those are partly responsible for heightened oxidative stress in cancerous cells [65,98-102].

In case if fructose is cut down the healthy cells that do not have access to ample oxygen, with having compromised aerobic breakdown of glucose would lead to death because of energy crisis, providing cancerous cells benefit of survival under supportive conditions to supersede healthy cells in number, suppressing the healthy cells functional networks, giving cancerous cells opportunity to spread to cause metastasis [65,101]. Fructose with ample and sustainable supply of minerals such as copper, superoxide dismutase (sod1p), glutathione (GSH), chelating agents and peptide transporters can provide a wise-integrated-food-therapy-based-components supporting healthy cells repairing phenomena and normal growth driving systems while arresting growth and initiating pre-death events in cancerous cells.

Cancer cells have a more acidic extra-cellular environment and a slightly alkaline intra-cellular environment. Cancer cells have higher levels of dissociated ions particularly iron and copper ions, inactive superoxide dismutase (sod1p) molecules (apo form or complete holo-molecules under scarcity of oxygen and in presence of carbon dioxide are deficient in dismutase activity) and glutathione (GSH), with ample sustainable supply of energy obtained by both metabolizing fructose and glucose sugars at the same time under hypoxia condition with having cellular cholesterol bio-synthesis levels minimized, making cell-to-cell-contact-inhibition compromised, leading to enhance fluidity of cell membranes enabling cancerous cells to migrate within tissues and across tissues and organs facilitating metastasis phenomena [103].

The cell membrane cholesterol levels play critical role in resisting deformability potential of cells (high cell membrane cholesterol levels increases the rigidity), in regulating oxygen (O_2), nitric oxide (NO) and carbon dioxide (CO_2) permeability across cell membranes altogether effecting micro-rheological characteristics of cells, potential of cells to aggregate including red blood cells (RBCs) as it is evident in patients of diabetics, obese people and patients having sickle cell disease or thalassemia which are characterized by low plasma high-density lipoprotein cholesterol levels (plasma HDL levels), high red blood cells (RBCs) membrane cholesterol levels and low blood levels of lipophilic antioxidants [57,58]. Microbiome has critical role in regulating cholesterol metabolism [80-82].

Intra-cellular cholesterol levels is increased in cancer cells but it undergoes oxidation under high oxidation stress, diminishing its role in sustaining the rigidity of cancer cells [94]. Intake of fructose (do not require insulin for entry in target cells) by cancer cells may increase the cellular cholesterol bio-synthesis levels, followed by its oxidation, enhancing cancer cell membrane fluidity permeability and mobility as an outcome inhibiting their cell-to-cell-contact-inhibition characteristic because cancer cells are deficient in un-oxidized-cholesterol-based-structure responsible for their structural integrity as a consequence of intra-cellular structural and plasma membrane cholesterol extensive oxidation that is indirectly facilitated by interrupted supply of copper ions and free oxygen to cancer transforming cells, leading to acquiring insulin-resistance while shifting the paradigms of metabolism and energy dynamics in cancerous cells [104-107].

Intake of whole minimal boiled eggs (put eggs in boiling water, hold them for 2.5 minutes and give them to patient after de-shelling them) several times a day, provides readily available source of essential amino acids, cholesterol and conjugated-minerals for cells of the patient's body, helpful for progeny cells emerging from cancerous cells to regain their native cellular features and for healthy cells to evolve in well-adopted cellular phenotypes, as an outcome builds first-line of resistance against mobilization of cancer cells facilitating metastasis [108,109].

Food therapy-restoring physiological homeostasis and pH in cancer cells

Cancer cells exhibits distinct micro-environment as compared to normal cells, characterized by a more acidic extra-cellular environment and a slightly alkaline intra-cellular environment. This reversed pH gradient is partly responsible for cancer cell behavior, including proliferation, fluctuating metastasis, and drug resistance by effecting sustainable minerals particularly copper ions supply, by differently altering roles of superoxide dismutase (sod1p), glutathione (GSH), intra-cellular iron ions, particularly intra-cellular copper ions, both in associated and dissociated forms, in addition to effecting cellular cholesterol bio-synthesis levels and altering cellular carbohydrate metabolism modes and levels by modulating underlying molecular processes including those involved in combating heightened oxidative stress and facilitating repairing phenomena which is regulated epigenetically by involving different inter-dependent-genes-operation-regulatory-networks, in addition to reverting shifts in pH and homeostasis of cancer cells, presenting food, being the source of these key players and influencers of cells' functions and fate, as an appropriate candidate to drive individualized-food-based-therapy or can be used for adjuvant therapy [110-117].

As already mentioned earlier, cancer cells have heightened levels of oxidative stress, hypoxia, altered pH, high energy demand, uncontrolled growth, high levels of copper and iron pools, superoxide dismutase (sod1p), glutathione (GSH), normal to higher cellular cholesterol bio-synthesis levels with acquired potentials to use insulin-dependent-sugars such as glucose (require insulin for entry in target cells) and insulin-independent-sugars such as fructose (do not require insulin for entry in target cells) to fulfill additional and diverse requirements of energy, nutrients and structural and functional precursors. The heightened cellular cholesterol bio-synthesis levels is associated with its increased accumulation on cells' plasma membranes but in oxidized form, preventing extra-cellular transport of many but not all micro-molecules and dissociated minerals ions leaching from their respective intra-cellular pools enabling them to pass across the cells' plasma membranes as the permeability of cell membranes increases with oxidation of cholesterol [118-122].

Despite of increased superoxide dismutase (sod1p), molecules levels, superoxide dismutase (sod1p), enzymatic activity is compromised in cancer cells because superoxide dismutase (sod1p) molecules, require sustainable ample free oxygen and copper ions supply to sustain their dismutase enzymatic activity whereas high oxidative stress and alkaline pH in presence of carbon dioxide confer peroxidase role on superoxide dismutase (sod1p) molecules, but diminish dismutase enzymatic activity of superoxide dismutase (sod1p) molecules partly, by converting them in copper ions deficient form such as apo form. Apo form of superoxide dismutase (sod1p) molecules enhances heterogeneity (cell-to-cell variability) in the cancerous clone conferring potential to escape growth limiting barriers and promotes cancer cells survival as an outcome superseding healthy cells in number [16,123-127]. Parallel to this, under hypoxia condition, in presence of carbon dioxide, superoxide dismutase (sod1p) molecules' peroxidase activity enhances and as an outcome cancer cells acquire the potential to use insulin-independent-sugars such as fructose (do not require insulin for entry in target cells) as source of nutrient and energy without releasing copper ions from superoxide dismutase (sod1p) molecules, unlike when they act as dismutase facilitating the biochemical reactions releasing copper ions [10,31-33,99,128,129].

Food therapy-iron copper associated and dissociated ionic equilibrium balance and cholesterol oxidation

Rich iron pools enhance cholesterol synthesis which is subsided under sustainable adequate supply of copper confirming role of copper deficiency in impaired energy production, abnormal glucose and cholesterol metabolism, increased oxidative damage, increased tissue iron (Fe) accrual, altered structure and function of circulating blood and immune cells, abnormal neuro-peptide synthesis and processing, driving persistent impaired effects on the immune system. As far as cancer is concerned, in later stage when there is high accumulation of free copper and iron ions with an increased carbon dioxide levels, peroxidase role of superoxide dismutase (sod1p) molecules in presence of iron ions under hypoxia conditions at alkaline pH enhances oxidation of cholesterol molecules leading to increase in fluidity of cell membranes and other cellular structures facilitating the process of metastasis [10,31-33,115,129-137].

Intra-cellular cholesterol supplementation by diet, such as by consuming minimal boiled eggs, can provide effective means for sustainable supply of cholesterol to cells, helpful to resist undergoing evolution progression process leading to generation of cancerous cells and to resist mobilization of cancer cells by replacing the oxidized intra-cellular and plasma membrane cholesterol with cholesterol obtained from diet.

Apoptosis is epigenetically driven process of death requiring glutathione (GSH), superoxide dismutase (sod1p) molecules in apo form with sustainable ample supply of free oxygen. Heightened levels of superoxide dismutase (sod1p) molecules with functional dismutase enzymatic activity resists initiation of apoptosis. Superoxide dismutase (sod1p) has additional role in regulating cholesterol metabolism through regulating energy flow and sensing micro-nutrients connecting neurophysiology with muscles altogether through regulating mitochondrial respiration. In cell membranes, cholesterol and sphingolipids structures carry proteins which control potassium (K) sodium (Na) levels and pH [138-140].

There are varieties of antioxidants which inhibit reactive oxygen species (ROS) formation, confirming that glutathione (GSH) loss is independent from the generation of reactive oxygen species (ROS). However glutathione (GSH) depletion is necessary for reactive oxygen species (ROS) generation. Interestingly, high extra-cellular thiol levels (systemic glutathione (GSH) and N-acetyl-cysteine levels) inhibits apoptosis, whereas, inhibition of reactive oxygen species (ROS) generation by antioxidants is ineffective in preventing cells death. It is established that glutathione (GSH) depletion is necessary for the progression of apoptosis activated by both extrinsic and intrinsic signaling pathways. This confirms a necessary and critical role of glutathione (GSH) loss in apoptosis and clearly uncouples glutathione (GSH) depletion from reactive oxygen species (ROS) formation by bifurcating the metabolic pathways those are being regulated genetically from associated metabolic pathways which are being regulated epigenetically by modulating interconnected programmed genes networks operations regulation [141].

Reduced glutathione (GSH) is hypothesized to play a role in rescuing cells from apoptosis in epigenetically driven manner, by buffering an endogenously induced oxidative stress as in absence of glutathione (GSH), superoxide dismutase (sod1p) molecules cannot gain copper ions, pre-requisite for sustaining aerobic respiration. In addition to this, availability of copper ions in cells is also dependent on glutathione (GSH) levels [142,143].

Glutathione (GSH) depleted cells do not undergo apoptosis in epigenetically driven manner suggesting redox status of cells is one of the key factors modulating apoptotic pathway in which glutathione plays a critical role in mediating apoptosis via nitric oxide (NO) and reactive oxygen species (ROS) boost; superoxide dismutase (sod1p) molecules by virtue of their apo form, (superoxide dismutase (sod1p) molecules devoid of copper ions) facilitate apoptosis in epigenetically regulated manner, for which they require glutathione (GSH) and sustainable ample supply of oxygen at physiological pH. This condition is subsided to facilitate survival of evolving cancerous cells [10,144,145].

Glutathione (GSH) modulates copper intake in cells. Copper uptake in cells decreases with decrease in glutathione (GSH) levels which in turn modulates the aerobic respiration and oxidative stress in presence sustainable ample supply of oxygen and regulate the apoptosis process in genetically or epigenetically driven manner depending on cells' homeostasis status, pH, availability of copper, oxygen, glutathione (GSH), dismutase activity of superoxide dismutase (sod1p) molecules and their levels, carbohydrate metabolism modes and levels and types of metabolizing sugars [146]. This confers a distinct role on copper for rescuing cells from escaping genetically or epigenetically driven apoptosis and as an outcome preventing their progenies to evolve as cancerous cells.

Published work indicates that only some reduction in cellular cholesterol bio-synthesis levels occurs with glutathione (GSH) deficiency [147]. A decrease in intra-cellular glutathione (GSH) levels allows an increase in plasma membrane cholesterol levels and a decrease in cholesteryl-ester content accumulation, which in turn results in enhancing tetrofosmin (TFOS) levels due to increased membranes'

permeability as an outcome of considerable cholesterol content accumulation in plasma membranes in cholesterol-molecules-oxidized-form, modulating cellular uptake potentials and their associated biological processes and events. The glutathione (GSH) status of the cells plays an important role in modulating plasma membrane cholesterol composition [148]. In addition to buffering intra-cellular and plasma membrane cholesterol oxidation, glutathione (GSH) generally also prevents other lipid peroxidation to certain extend [149].

In presence of high level iron pools, cells are prone to undergo epigenetically programmed ferroptosis (cell death) due to uncontrolled cell membrane lipid peroxidation where glutathione (GSH) plays a critical role in preventing it by exhibiting its multifaceted roles [125,127,150-157].

In cancer cells, high levels iron pools, high levels of glutathione (GSH) and superoxide dismutase (sod1p) molecules, in presence of carbon dioxide (CO_2) under hypoxia drive the cells to switch to un-programmed genomic paradigm escaping from epigenetically driven programmed ferroptosis or genetically driven programmed apoptosis leading to uncontrolled growth of progeny cells lacking native characteristics with genetic variations and shift in genes networks operation regulation paradigms emerging as cancerous cells or their parent cells.

Genes, their products' relation with genes networks operations regulation, cancer and metastasis-A brief view

As stated earlier, classical hypothesis about cancer and its relation with mutations and shifts in genes networks operations regulation preliminary governed by inherited or somatic alteration in genes has changed since the findings reported by Rab in 2007 over twenty years ago which are yet unpublished [10].

Cancer cells exhibit heightened oxidative stress, hypoxia, altered pH, high energy demand, uncontrolled growth, a more acidic extra-cellular environment and a slightly alkaline intra-cellular environment, high levels of copper and iron ions, high levels of superoxide dismutase (sod1p) and glutathione (GSH), normal to higher biosynthesis levels of intra-cellular and plasma membrane cholesterol with acquired potentials to use insulin-dependent-sugars such as glucose (require insulin to enter in target cells) and insulin-independent-sugars such as fructose (do not require insulin to enter in target cells) to fulfill additional and diverse requirements of energy and to provide nutrients and structural and functional precursors [86,87,93-97].

Cancer cells are reported to have high extra-cellular (systemic) thiol levels (glutathione (GSH) and N-acetyl-cysteine) which seems to be one of the reasons to prevent apoptosis process in epigenetically driven manner that can occur in genetically modulated manner under sustainable ample supply of oxygen and copper in response of depletion of glutathione (GSH) even without shifts in oxidative stress. However unlike healthy cells, glutathione (GSH) depletion alone is not driving factor to initiate apoptosis process in cancerous cells [143].

As briefly discussed earlier, glutathione (GSH)/glutathione disulfide (GSSG) (GSH/GSSG) pair controls the copper transport pathway by regulating the redox state of a copper chaperone Atox1 (human copper metallochaperone protein). Glutathione disulfide (GSSG) mediates oxidation of copper-coordinating cysteine residues in Atox1 molecules with the formation of an intra-molecular disulfide. Glutathione (GSH) alone is sufficient to reduce disulfide bonds, restoring the ability of Atox1 (human copper metallochaperone protein) to bind copper. This reaction is facilitated by glutaredoxin 1 (GRX1) when glutathione (GSH) levels is low. Cellular high glutathione (GSH) levels both reduces Atox1 (human copper metallochaperone protein) and is required for cell viability in the absence of Atox1 (human copper metallochaperone protein). In turn, Atox1 (human copper metallochaperone protein), which has a redox potential similar to that of glutaredoxin, becomes essential for cell survival when GSH levels decreases. Atox1 (human copper metallochaperone protein) (+/+) cells resist short term glutathione (GSH) depletion, whereas Atox1 (human copper metallochaperone protein) (-/-) cells under the same conditions are non viable because superoxide dismutase (sod1p) molecules become copper deficient and as an outcome, lacking their dismutase enzymatic activity. Apo form of superoxide dismutase (sod1p) molecules initiates apoptosis in epigenetically driven manner, a process which is vanished in cancerous cells because of acquired peroxidase activity by superoxide dismutase (sod1p) molecules without

losing the attached copper ions in presence of carbon dioxide (CO_2) under hypoxia at alkaline pH enabling the cancerous cells to use glucose as well as fructose as sources of energy, nutrients and as functional and structural precursors, supporting cancerous cells survival [142].

Presence of high levels of iron pools can promote lipid peroxidation. Accumulation of high levels of iron pools, as it happens in cancer cells, facilitates lipid peroxidation driven inflammatory response, inflammation-involved cognitive and immunological dysfunction including autoimmune response, an associated feature of various therapies including chemotherapy [158-171].

In addition, lipid peroxidation facilitates the process of generation of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE) and other lipid peroxidation products at high levels. Glutathione (GSH) inhibits lipid peroxidation by scavenging lipid peroxides through glutathione peroxidase 4 (Gpx4) and inhibits ferroptosis. Glutathione (GSH) can prevent oxidation of cholesterol but it does not directly bind with oxidized cholesterol products, revealing its selective reactivity with other oxidized lipid products, providing a chemically driven escape for cells to evolve as well-tailored cellular phenotypes with or without having potentials to undergo aging by targeting the genes regulatory operations networks, driving cellular cholesterol bio-synthesis levels and its feedback regulatory loop modulated by oxidized cholesterol levels enabling cancerous cells to undergo metastasis [172-180].

The glutathione (GSH) levels regulates cell cycle and rate of cell division, cells in growth 1 phase (G1) undergo a transient nuclear peak of glutathione (GSH) levels prior to co-ordinated entry into synthesis phase (S phase) of cell cycle, followed by rapid cells divisions and cellular re-programming [16]. Inter-connected blocks of the ground tissues impair regeneration process, which is rescued by exogenous systemic glutathione (GSH). It is inferred that glutathione (GSH) present in body fluids and/or from the outer tissues is released upon injury, licensing an exit of cells in growth 1 phase (G1) near the wound to induce rapid cell division and re-programming [16,181-183].

Lipid peroxidation can be prevented to certain extend by glutathione (GSH) whereas the end products of lipid peroxidation is captured by glutathione (GSH). Oxidized cholesterol products do not bind with glutathione (GSH) giving cancer cells benefit of survival. Cancer cells have high level pools of glutathione (GSH) with heightened cellular cholesterol bio-synthesis levels but accumulating intra-cellular cholesterol in oxidized form and as an outcome oxidized cholesterol remains un-reacted with glutathione (GSH), effecting the copper transport across target cells by altering the functions of cell-membrane-copper-transporter-proteins, separating the genetically programmed functions and epigenetically programmed functions' paradigms of cells from their acquired un-programmed functions, unlike the healthy cells, operating only on programmed paradigms. High levels of glutathione (GSH) in cancer cells may partly account for their rapid and uncontrolled growth [158,184-188].

High levels of glutathione (GSH) and its diverse roles in normal and cancerous cells

The multiple roles of glutathione (GSH) are altered in cancerous cells partly as an outcome of cancer cells' functions are majorly being regulated by un-programmed paradigms under altered given conditions and environment with limited operations regulated by sustained genetically and/or epigenetically driven programmed cellular functions.

Cancer cells cope with high oxidative stress levels, characterized by a equilibrium shift to producing glutathione disulfide (GSSG), oxidized product of glutathione (GSH) in the redox couple glutathione disulfide (GSSG)/reduced glutathione (2GSH) (redox couple) (GSSG/2GSH). Under these conditions, the cytosolic copper chaperone Atox1 (human copper metallochaperone protein), which delivers copper (1) ion [Cu(I)] to the secretary pathway, is oxidized, such as, a disulfide bond is formed between the cysteine residues of the copper (1) ion Cu(I)-binding CxxC motif. Switching to the covalently-linked form, sulfur atoms are no more able to bind copper (1) ion Cu(I) ion and Atox1 (human copper metallochaperone protein) cannot play an antioxidant role [189,190]. Copper levels are higher in cancer cells which seem to be also contributed by higher levels of superoxide dismutase (sod1p) molecules.

Therapeutic targeting copper levels in cancer is not an appropriate strategy as with shifts in copper levels can generate superoxide dismutase (sod1p) apo molecules high level pools responsible for further increasing heterogeneity (cell-to-cell variability) in cancerous cells enabling them to resist epigenetically driven death process initiation with acquiring the potential to evolve in more well-adopted cellular phenotypes possessing cancerous characteristics while inhibiting aging process whereas in neighboring healthy cells, shifts in copper levels can boost oxidative stress while arresting their growth, facilitating the initiation of epigenetically driven apoptosis process mediated by heightened levels of superoxide dismutase (sod1p) apo molecules.

Cancer cells have intra-cellular alkaline pH whereas outer environment of cancer cells has acidic pH. Under these conditions apoptosis process shuts down due to acquired superoxide dismutase (sod1p) molecules' peroxidases activity, sustaining their structural stability with heightened peroxidase activity levels but lacking dismutase activity (catalyzes the dismutation of the superoxide anion into hydrogen peroxide and molecular oxygen) under hypoxia and in presence carbon dioxide (CO_2). Targeting copper levels can further intensify the uncontrolled growth of cancer cells and their dispersion in response of heightened levels of cellular structures and plasma membrane oxidized cholesterol molecules, effecting cells' rigidity, integrity and permeability [9,10,16,125-127].

Shift in *SOD1*-Sod1p role drive unusual complication features associated with therapies including chemotherapy

To look into a given scenario with a different prospective related to effect of therapies including chemotherapy, it is necessary to re-visit features of micro-environment of cancer cells. As mentioned earlier, in addition to heightened oxidative stress, cancer cells have intra-cellular alkaline pH whereas outer environment of cancerous cells is acidic. Under these conditions, apoptosis process shuts down as an outcome of acquired peroxidase activity by superoxide dismutase (sod1p), sustaining its structural stability composing superoxide dismutase (sod1p) molecules pools in high levels but lacking dismutase activity (catalyzes the dismutation of the superoxide anion into hydrogen peroxide and molecular oxygen) under hypoxia and in presence carbon dioxide (CO_2). Speaking in terms of molecular biology, superoxide dismutase (sod1p) molecules act as peroxidase in the presence of hydrogen peroxide (H_2O_2) at high pH (pH > 9). Superoxide dismutase (sod1p) molecules 'peroxidase activity involves generation of hydroxide ion (.OH) at the copper site without releasing copper ions from the enzyme. Released hydroxide ions (.OH) radical is proposed to attack histidine residues that are crucial for copper binding to superoxide dismutase (sod1p) molecules, driving boost in oxidative stress coupled with inactivation of dismutase activity, in addition to causing autoimmune response, one of the consequences of extensive cells destruction in absence of superoxide dismutase (sod1p) molecules' ample dismutase activity. This is one of the main reasons for causing fluid accumulation in cancer therapy, facilitating water retention in lungs associated with heart failure as fluid removal of the body is dependent on *SOD1* gene operation network regulation and levels of dismutase activity exhibited by superoxide dismutase (sod1p) molecules under sustainable ample supply of free oxygen and copper while utilizing glucose as a source of energy and nutrients [27,31,125,193-203].

Superoxide dismutase (sod1p) by virtue of its peroxidase activity promotes the process of oxidation, driving shifts in oxidative stress under hypoxia condition in presence of carbon dioxide at alkaline pH, responsible for halting aging process in cancer cells in response of multiple ongoing unusual biological events in the cells particularly compromising the role of glutathione (GSH) in preventing oxidation of heightened level of cellular bio-synthesized cholesterol molecules incorporated in cellular structure and in plasma membranes responsible for increased rate and uncontrolled growth in cancer cells [16].

As already discussed elsewhere, high iron levels in cancer cells inhibits sustainable supply of copper that further enhances oxidative stress and intensifies oxidative stress driven consequences. The iron copper levels both associated and dissociated ionic equilibrium balance modulate cells destruction events including ferroptosis, cuproptosis, apoptosis, autophagy, necroptosis and pyroptosis and their inhibition [204,205].

Iron and glutathione (GSH) levels are inter-related, initially increase in iron levels causes an increase in intra-cellular glutathione (GSH) bio-synthesis levels leading to generate heightened glutathione (GSH) content levels but later on in response of shifts in pH and sustained progressive fluctuations in homeostasis it causes depletion in glutathione (GSH) (reduced form) levels coupled with an increase in glutathione disulfide (GSSG) (oxidized form) levels while impairing cells' integrity [206,207].

Glutathione disulfide (GSSG) (oxidized form) is reduced by nicotinamide adenine dinucleotide phosphate (NADPH) when fructose is used as a source of nutrients and energy by cancer cells in parallel to glucose, unlike healthy cells, helpful to combat boosting oxidative stress in cancer cells while providing energy and nutrition to cancer cells. It provides broader venue for fructose to be used as a source of nutrients and energy and to combat oxidative stress in parallel in cancer cells but at the cost of copper levels deficiency progression [208-212].

These features are missing in healthy cells and as an outcome depletion of glutathione (GSH) initiates apoptosis process in healthy cells by epigenetically driven manner leading to their death in case if the cells' conditions do not support them to undergo genetically or epigenetically driven programmed evolution, escaping the apoptosis process.

Atox1 (human copper metallochaperone protein)'s copper-binding site's sensitivity to cellular redox environment is crucial for copper loading into superoxide dismutase (sod1p) molecules when the primary plasma membrane copper transporter, copper transporter 1 (Ctr1p) is not functional as it can happen in cancer cells, in response of losing cellular structures' integrity including cell membranes, effecting the functions of cell membranes proteins including transporter proteins such as copper transporter 1 (Ctr1p). This confers an additional role on Atox1 (human copper metallochaperone protein) molecules, particularly in cancer cells to act as a junction bridge molecule connecting genetically and epigenetically driven programmed cellular functions with acquired un-programmed cellular functions attained by transformed cells behaving as cancerous cells regulated by altered or un-programmed genes networks driven operations [9,10,15-18,142].

Ferroptosis is epigenetically driven programmed death. Ferroptosis and lipid peroxidation are closely linked; lipid peroxidation is the driving stimuli behind ferroptosis. Ferroptosis is characterized by iron-dependent-lipid-peroxidation. The most critical target of this iron-dependent-peroxidation in membranes are cholesterol molecules, effecting the cells membranes' integrity, leading to initiation of genetically driven cells' death or evolution of cells with environmentally well-tailored cellular phenotypes in healthy cells under sustainable ample supply of copper ions and free oxygen whereas in case of cancerous cells, under scarcity of oxygen and glucose, in presence of carbon dioxide, ferroptosis is escaped in spite of having high levels iron pools because of selective action of glutathione (GSH) molecules for engaging oxidized lipid molecules but sparing oxidized cholesterol molecules leading to altered permeability of cell membranes, functions of cell membranes' proteins including transporter proteins such as copper transporter 1 (Ctr1p) while diminishing sustainable copper supply to cells [9,10,15-18,142,150,213-219]. In addition to this, glutathione (GSH) molecules are responsible for increase in growth rate and indirectly play a critical role in enhancing heterogeneity (cell-to-cell variability) of cancer cells, supporting survival of competing cancer cells over healthy cells. For this reason ferroptosis cannot be used as a cancer therapy strategy as in response healthy cells would be targeted more intensely than cancer cells, enhancing metastasis process.

In order to undergo ferroptosis, sustainable ambient aerobic respiration, supporting bioenergetics of cells is pre-requisite. Lipid peroxidation (LPO) is initiated by alkoxyl radicals produced by ferrous iron from the hydroperoxide derivatives of lipids (LOOH), whose traces are generated in response to aerobic metabolism. Ferroptosis takes place when a threshold has been exceeded. This occurs when the major conditions are satisfied: i) oxygen metabolism leading to the continuous formation of traces of hydroperoxide derivatives of lipids (LOOH) from phospholipid containing polyunsaturated fatty acids; ii) missed enzymatic reduction of hydroperoxide derivatives of

lipids (LOOH); iii) availability of ferrous iron from the high levels iron pools. Yet, when the homeostatic control of the steady state between lipids and hydroperoxide derivatives of lipids (LOOH), such as hydroperoxide derivatives of lipids (LOOH) formation and reduction, is lost, for instance, in scarcity of antioxidants, lipid peroxidation (LPO), such as oxidation of cholesterol molecules is activated, initially, arresting the cells' growth [103], eventually destructing the cells' integrity by damaging the cell membranes and driving execution of ferroptosis, causing cells death [150,151,220-222] but in cancer cells due to scarcity of oxygen and copper under energy crisis in the presence of carbon dioxide (CO_2) at alkaline pH, peroxidase activity of superoxide dismutase (sod1p) molecules catalyzes the production of nicotinamide adenine dinucleotide phosphate (NADPH) [223] and same can happen in parallel, such as production of nicotinamide adenine dinucleotide phosphate (NADPH) by metabolism of fructose in cancer cells. Fructose metabolism in cancer cells can generate nicotinamide adenine dinucleotide phosphate (NADPH), primarily through the pentose phosphate pathway (PPP) [65,224,225] combating the oxidative boost and enabling cancer cells to escape ferroptosis by establishing homeostatic control of the steady state between lipids and hydroperoxide derivatives of lipids, (LOOH) facilitating cells to evolve with altered cellular phenotypes with or without undergoing the aging process as an outcome of losing conserved genetic makeup.

Fructose cannot be used as a target molecule for treatment of cancer, as in response survival of cancer cells would be favored, enhancing their number more rapidly as compared to healthy cells that are facing energy and nutritional crises while struggling to resist their growth arrest.

Ferroptosis is recently acknowledged as a form of epigenetically driven programmed cell death distinct from apoptosis, necrosis, and autophagy. It is characterized by the accumulation of high levels iron pools and lipid peroxidation in cells, causing oxidative damage with eventual destruction of cellular membranes. [150]. Compounds, complexes, suspensions, mixtures etc. from natural and biologically originated sources such as food, particularly desi food, can modulate, for instance, can initiate, inhibit, or alter ferroptosis process driven consequences, confirming role of food in preventing and curing a wide range of diseases [226].

The high levels iron pools facilitate uncontrolled cancer cells' growth partly by ceasing the dismutase activity and mainly by acquiring peroxidase activity by superoxide dismutase (sod1p) molecules under hypoxia conditions, in the presence of carbon dioxide at alkaline pH. Shifts in oxidative stress coupled with an increase in glutathione (GSH) synthesis turnover leading to an increase in glutathione (GSH) and iron levels, but causes decrease in available copper levels eventually mediates fluctuation in pH which then disrupts homeostasis and depletes glutathione (GSH); in response to further increase in iron levels associated with an increase in glutathione disulfide (GSSG) (oxidized form) altogether, impairs cell integrity and cellular functions. Under these conditions, some of the cells' progenies evolve as cancerous cells having potential to use fructose as a sugar for source of energy and nutrition as well as glucose for same purposes, though initially it causes an increase in oxidative stress, but in later stage, fructose utilization under heightened oxidative stress and hypoxia at alkaline pH leads to a decrease in oxidative stress, enabling cells to undergo uncontrolled growth due to the acquired oxidase activity by superoxide dismutase (sod1p) molecules, in the presence of carbon dioxide and high iron levels pools, over expressing *SOD1* gene affecting the genes' operation regulation within its network of genes and its associated networks of genes in an epigenetically driven manner, facilitating the un-programmed intra-cellular and inter-cellular regulation of cancer cells [9,10,15-18,29,31-33,123,206-212,227-231].

These bio-circuits provide a broader venue for fructose to be used as a source of energy and to combat oxidative stress but at the cost of copper deficiency progression, providing a cushion for cells' multiple evolutionary pathways while escaping programmed cell death execution. In parallel to this, high levels of iron pools initiate an autoimmune response, transferring the consequences of changes in the cellular micro-environment to physiological systemic levels at advanced stages, a consequence that is evident in the response to therapies, particularly chemotherapy [193].

Glutathione (GSH) and genes networks operations regulation-cells death vs evolution of variants and therapy's prospects

Glutathione (GSH) plays multiple roles in cells. Glutathione (GSH) is a substrate for multiple enzymes that remove reactive oxygen species (ROS). Copper and iron can catalyze glutathione (GSH) oxidation, that oxidizes reduced glutathione (GSH) to oxidized glutathione disulfide (GSSG) to reduce the levels of glutathione (GSH). In healthy cells, depletion of glutathione (GSH) makes cells more sensitive to harmful stimuli, strengthens the cytotoxicity of reactive oxygen species, and makes metals intensely catalytic, facilitating epigenetically driven cells death. Targeting glutathione (GSH) as a strategy for cancer therapy is not appropriate, as in response healthy cells would be targeted more intensely as compared to cancer cells, for the reasons already discussed earlier [204,231,232].

High levels intra-cellular glutathione (GSH) pools are associated with apoptotic-resistant cellular phenotypes, facilitating cells to evolve as well-tailored cellular phenotypes in epigenetically driven manner by altering the regulation of genes networks operations. Glutathione (GSH) depletion by itself either induces or stimulates apoptosis in healthy cells [233-236].

It was revealed over two decades ago but has been recently experimentally established that ferroptosis driven by the accumulation of high levels of iron pools requires sustainable supply of free oxygen and dismutase activity possessed by superoxide dismutase (sod1p) molecules at physiological pH, changing the classical understanding in this domain of knowledge [4,5,9,10,15,16,34-41]. It confirms that ferroptosis is a programmed epigenetically driven death process that occurs in healthy cells when cells sustain their programmed genes networks' operation regulation functional [237-240].

The generation of reactive oxygen species (ROS) and subsequent hydroxyl radical (·OH)-mediated lipid peroxidation culminating with plasma membrane damage are the core events causing ferroptosis [239]. These processes are inhibited by integrated-systems such as antioxidant systems integrated with membrane repairing systems. In case of having non-functional plasma membrane copper transporters or in their absence, glutathione (GSH) acts as a copper shuttle, transporting copper to superoxide dismutase (sod1p) molecules; and facilitating their oxidase role under hypoxia, in presence of carbon dioxide (CO_2), at altered pH and disturbed homeostasis, as it happens in cancer cells and in many other diseases [241-246].

Glutathione (GSH) may also be involved in transporting copper to superoxide dismutase (sod1p) molecules when *CTR1* gene encoding copper transporter 1 (Ctr1p) protein is down-regulated or non-functional in humans, substituting the role of the yeast *LYS7* genes' product [4,5,9,10,15,16,34-41,146]. These cell membrane antioxidant pathways integrated with cell membrane transport systems can be a good target for cancer-therapy-integrated-food therapy.

As already discussed earlier though depletion of glutathione (GSH) activates apoptosis, but targeting glutathione (GSH) for cancer therapy is not an appropriate strategy as its going to deplete glutathione (GSH) from healthy cells as well, causing switching off superoxide dismutase (sod1p) molecules' dismutase activity associated with over expression of *SOD1* gene, placing cells in an micro-environment built up of high levels of iron pools, with switching on programmed option to use fructose as source of energy with glucose whose utilization decreases with increasing hypoxia and accumulation of carbon dioxide (CO_2) facilitating evolution of environmentally well adopted cellular phenotypes with or without aging deficient in superoxide dismutase (sod1p) molecules' dismutase activity, whose daughter progenies can become parent cells for cancer cells [9,10,15-18,29,31-33,123,206-212,227-231,247].

Many reactive oxygen species (ROS) defense processes depend on the tri-peptide glutathione (GSH) molecules, which constitutes a junction molecule bridge connecting genetically regulated cells' programmed functions and epigenetically regulated programmed functions with newly evolved un-programmed genetically and epigenetically driven cellular functions and their inter-dependent operations regulation in variants and in transformed cells; some of them may become parent cells for cancerous cells [248].

In cancer cells, intra-cellular basic environment seems to play a key role in de-protonating thiol group (-SH) of cysteine, forming a thiolate anion (S-). This conversion to thiolate form significantly alters cysteine's reactivity, anti-oxidative role, and various other roles in biological processes [33,54,249-252]. Glutathione (GSH) molecules' enzymatic deficiency can slightly decrease the cellular cholesterol bio-synthesis turnover [147]. It is for earlier discussed reasons, minimal boiled eggs intake on regular basis (preparation procedure has been discussed elsewhere) can play therapeutic role in cancer illness. Eggs play a critical role in trapping free iron pools, in providing proteins rich in cysteine, and in repairing cells through cellular cholesterol re-structuring, that supports healthy cells growth and enables them to compete with cancer cells while limiting their growth. Among many proteins of egg origin, the important one is ovotransferrin (also known as conalbumin), a different protein rich in cysteine that binds with free iron. Ovotransferrin, a transferrin family member, is the major iron-binding protein in egg white that helps to limit iron availability, reverting initiation of cancer-propagating biological events. In addition to providing instant source of energy and nutrients, minimal boiled eggs intake is helpful to manage post-chemotherapy or other types of therapies related sudden heart rate and/or blood pressure drop without any drug intervention [253].

As already mentioned earlier, certain food ingredients added in desi food and minimal boiled eggs can be used as food therapy for cancer patients because of their conserved prophylactic and therapeutic roles or can be used as an adjuvant therapy for treatment of a wide range of diseases, leading to complete cure without causing any side effects or complications in cost-effective manner.

Desi food, by virtue of its ingredients, processing, structural and organoleptic properties, offers a wide range of diversified food systems with variable physical chemistry dynamics (for instance mixture, suspension, emulsion, solution, etc.) both in hybrid and in respective manner which offer conservation of bioactive compounds and facilitate their transport to target cells and sites across the cells; many of them can pass across the blood-brain barrier, in addition to preserving beneficial microbes and resisting pathogens' proliferation, with acquired augmented potentials to boost appetite and to enhance their absorption in blood while stabilizing the mood. Desi food provides appropriate mediums for trapping and conserving bioactive compounds for ongoing bio-transformation processes, including fermentation generating novel bioactive chemical or biochemical entities having diverse prophylactic and therapeutic potentials that otherwise are not commonly available in nature. The presence of biologically originated chelating biochemical or chemical entities in desi food, particularly those which can pass across cells and blood-brain barrier, providing an additional means of delivering minerals and other ligands to the target sites while scavenging the free ions, contributing to stabilize disturbing homeostasis partly responsible for shifts in intra- and inter-cellular pH and oxidative stress.

The preliminary general scheme of desi food preparation has been reported by Abdur Rab and Hassan in 2022 [3]. However, modification as per requirements of patients, depending on the of illnesses, stage of disease, and associated complications, can be done when food is used as food therapy or food is used as an adjuvant therapy because of its prophylactic and therapeutic roles leading to complete cure.

Results and Conclusion

Many non-contagious diseases share the same interconnected programmed genomic or epigenetically driven molecular pathways leading to cause illness, as well as to deciding the fate of illness using oxidative stress shifts as an inducing stimuli for ongoing biological phenomena within or across the cells, a common consequence of injury and illness. It is evident from the earlier discussion supported by cited literature that food therapy can be used to treat a wide range of illnesses, leading to complete cure, and at the same time it can be used as a prophylactic agent for a wide range of diverse illnesses, in addition to its role as an adjuvant therapy. This piece of work reveals the missing understanding in the treatment strategies that are being used to treat most of the non-contagious diseases, including cancer.

This paper builds on current knowledge to reveal the underlying molecular mechanisms of illness, including their role in determining disease fate and complications, by sharing interconnected molecular pathways involving genetically and/or epigenetically-driven

phenomena This work suggests some universal food combination models, constituting food therapy, helpful to modulate the outcome of other therapies, particularly cancer therapies, leading to a complete cure in cost effective manner without risking patient's safety.

Food therapy is an un-revealed area of knowledge that offers treatments or supportive treatments to a wide range of currently incurable diseases, leading to complete cure in a cost-effective manner involving minimal risks to natural health or lives of consumers. After addressing the existing knowledge gaps, domains of knowledge relevant to food therapy, invite further investigation to reveal cure for many currently incurable diseases.

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