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Review

Trauma Induced Acute Redox Imbalance, the Filling Oxidant Sinks, and a Plausible Food as Medicine Solution

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Abstract: Trauma is a leading cause of death worldwide. While early deaths are most commonly from hemorrhage and direct organ injuries, delayed deaths are mostly caused by the fallout of inflammation, presumably induced by oxidative stress. Increasing evidence shows that many or most of the complications of trauma are also associated with oxidative stress. In this manuscript we review the current literature on trauma associated redox imbalance, bridging the gap between basic science research and clinical practice from a broad perspective. The triple oxidant sink metaphor is presented to give a visual gauge of how redox balance might be achieved. We then introduce a plausible multimodal redox balancing regimen, using food as medicine

Keywords: oxidative stress; food as medicine; whole plant food antioxidants; whole plant food fiber; redox imbalance; trauma.

1. Oxidative Stress/Redox Imbalance

The term oxidative stress most commonly refers to an imbalance of pro-oxidants and antioxidants resulting in a pro-oxidant predominance. Pro-oxidants may be in the form of excess free radicals, hydrogen peroxide (H_2O_2), or other pro-oxidant molecules in relation to the cell's/organism's antioxidant defense [1].

With an overabundance of highly reactive free radicals (reactive oxygen species (ROS) and reactive nitrogen species (RNS)), direct cellular injury results. Chain reactions from highly reactive free radicals continue until neutralized. Free radical direct hits can occur anywhere in the cell. In hydrogen peroxide derived redox balance problems, the dramatic direct cell injury is less, but the cells respond with production of inflammatory cytokines inducing downstream phenomena. The cytokine cascade alters local and, often, systemic inflammatory balance. Some mediators of this downstream inflammatory cytokine production include nuclear factor kappa-light chain-enhancer of activated B cells (NFκB), activated protein kinase pathway (AMP-K), and apurinic/apyrimidinic endonuclease 1/reduction-oxidation factor 1 (APE/Ref1) while nuclear factor erythroid 2-related factor 2 (Nrf2), among others, modulate and decrease inflammatory cytokine release. Downstream phenomena include alterations in vital cellular functions, inhibition and differentiation of progenitor cells, alterations in deoxyribonucleic acid (DNA), cell membrane changes, changes in energy metabolism, and even mitochondrial initiated cell death/apoptosis [1–3].

1.1. Sources of Free Radicals and Redox Imbalance

Mitochondria are the most common source of daily free radicals due to errors in electron transport occurring about 1–5% of the time [4,5]. Other cellular pathways that are responsible for production of free radicals and H_2O_2 include the NADP–NADPH cycle used in neutrophils for destruction of bacteria and viruses, xanthine oxidase

reactions during purine catabolism, nitric oxide synthase reactions in nitric oxide production, cyclooxygenases (COX) pathway for prostaglandin production, and cytochrome P-450 reactions, among others [4].

In spite of their destructive potential, ROS and RNS are needed for normal cellular functions as they are involved in cellular messaging regulating proliferation, differentiation, apoptosis, repair processes, gene transcription and transduction, adaptation to exercise, and destruction of foreign microbes [4,6]. Normal cellular function and communication depend on ROS and RNS so the goal is not to completely exterminate them, but rather to keep them in balance, preventing oxidative stress consequences.

Anything that increases the metabolic rate in the cell's mitochondria increases oxidative stress. Exercise [5], detoxifying of toxins or ethanol (cytochrome p-450) [7], cold exposure [8], high concentration oxygen environments [9], smoke inhalation (1st and 2nd hand cigarette smoke) [10], increased concentrations of sodium [11], heavy metals (including iron) [12], soft tissue injury [13], infections, and ischemia-reperfusion (IR) [14] are a few examples. Radiation [15,16], mental stress [17], and severe life stressors promote an oxidant state [18]. Lifestyle factors can affect redox balance as well including eating foods that do not carry naturally occurring antioxidants or fiber [19–21], hydration [22], sunshine (vitamin D levels) [23], and even lack of sleep [24].

Closely related to oxidative stress is endoplasmic reticulum stress (ER stress). ER stress is caused by misfolding of proteins in the ER, which affects protein function, further increasing the pro-oxidant balance of the cell. While ER stress increases oxidative stress, oxidative stress also increases the likelihood of protein misfolding and thus increases ER stress [25].

1.2. Neutralizing Oxidative Stress

ROS and RNS are neutralized by both intrinsic and extrinsic methods. The intrinsic mechanisms involve host antioxidant enzymes disarming the free radicals like superoxide dismutases, peroxidases, and others [26]. These enzymes are distributed throughout the cell.

The intrinsic non-enzymatic antioxidant defense is based on free radical scavengers. Glutathione is thought to be one of the most important non-enzymatic antioxidants [27]. Albumin, the most common protein in the body, serves as an abundant and important circulating free radical scavenger [28]. Albumin's disulfide bonds neutralize the dangerous pro-oxidant free radicals.

Extrinsic methods of oxidative stress neutralization include free radical scavengers and immunomodulators. Diet obtained free radical scavengers are classically compared by their oxygen radical absorption capacity (ORAC value) [29]. Each individual ORAC unit absorbs one free radical.

Immunomodulators are oxidative stress neutralizers that affect the downstream inflammatory cytokine, leukotriene, complement, prostaglandin production and/or promote increases in the body's endogenous antioxidant reserve [30]. The antioxidant responsive element (ARE), often stimulated by Nrf-2, promotes transcription of genes encoding endogenous antioxidants and other cytoprotective proteins. Immunomodulators include vitamin B_{12} [31] and D [23], sulforaphane (from broccoli and other cruciferous vegetables) [32], and many others.

The gut microbiome is another source of immunomodulation for oxidative stress. Short chain fatty acids (especially butyrate) formed by the healthy gut bacteria from fiber have been shown to be a significant factor in lowering oxidative stress [33]. Thus, antioxidants and fiber appear to be operational in scavenging free radicals, stifling the downstream cytokines and other inflammatory molecules, upregulating the body's endogenous antioxidant enzymes, and optimizing the redox balance of the entire organism.

Certain stressors on the body, like exercise, are initially pro-oxidants, but stimulate endogenous antioxidant production resulting in a net positive redox balance [34]. Intermittent fasting also stresses the body and thus increases endogenous antioxidant production [35]. Other hormetic stressors upregulate the expression of vitagenes (genes involved in cellular homeostasis during stressful conditions) which code for thioredoxins, sirtuins, and heat shock proteins. Vitagenes are associated with improved health and longevity and are also stimulated by polyphenols and flavonoids [36,37]. Negative pressure wound management systems (vacuum assisted closure–VAC) also induces local increases in superoxide dismutase, improving local blood flow [38]. Acute oxidative stress also causes increased endogenous antioxidants. The free radicals in the cell not only stimulate inflammatory cytokines, but also induce production of Nrf-2 [39]. This negative feedback loop stimulates the ARE and may be a cause of the inflammatory nadir near day 5 after severe trauma.

2. Triple Oxidant Sink Theory

The triple oxidant sink theory has been previously described and illustrated [40]. The essential concept in the triple oxidant sink theory is that every organism has a "sink" for absorbing the free radicals of ROS and RNS, hydrogen peroxide and other pro-oxidants. The sink allows for buffering of the deleterious effects of ROS and

RNS. The "depth" of this sink is determined by the genetically and stimulated complement of endogenous antioxidant capacity (enzymatic and non-enzymatic) and the available exogenous free radical scavengers and immunomodulators.

The oxidative state of an individual depends on lifestyle factors including: sleep patterns, baseline stress level, exercise routines, dietary antioxidant intake, environmental and food borne toxin load, individual microbiome composition, and many more. When that sink encounters small loads of free radicals or pro-oxidants, schematically seen as water in the sink, the sink of intrinsic and extrinsic antioxidants are able to disarm/detoxify them. The oxidant sink is able to protect the organism until that sink of oxidants is filled to capacity and overflows into the second sink, initiating damage that causes disease and pathophysiology. The specific disease that develops depends upon genetic predisposition and epigenetics—whether that is pre-diabetes, osteoporosis, depression, or heart disease, etc. When the second sink fills and overflows into the third sink complication of disease occurs. If the organism encounters a high level of inflammation from a severe trauma or sepsis, the oxidant sinks fill quickly and the organism becomes overwhelmed with free radicals, hydrogen peroxide, and other pro-oxidants that cannot be neutralized. If the sinks overflow completely, then SIRS (systemic inflammatory response syndrome) ensues injuring distant organs leading to acute respiratory distress syndrome (ARDS) and potentially multiple organ dysfunction syndrome (MODS). If oxidative stress continues or the organism cannot recover from the insult, the organism fails. (See Figure 1)

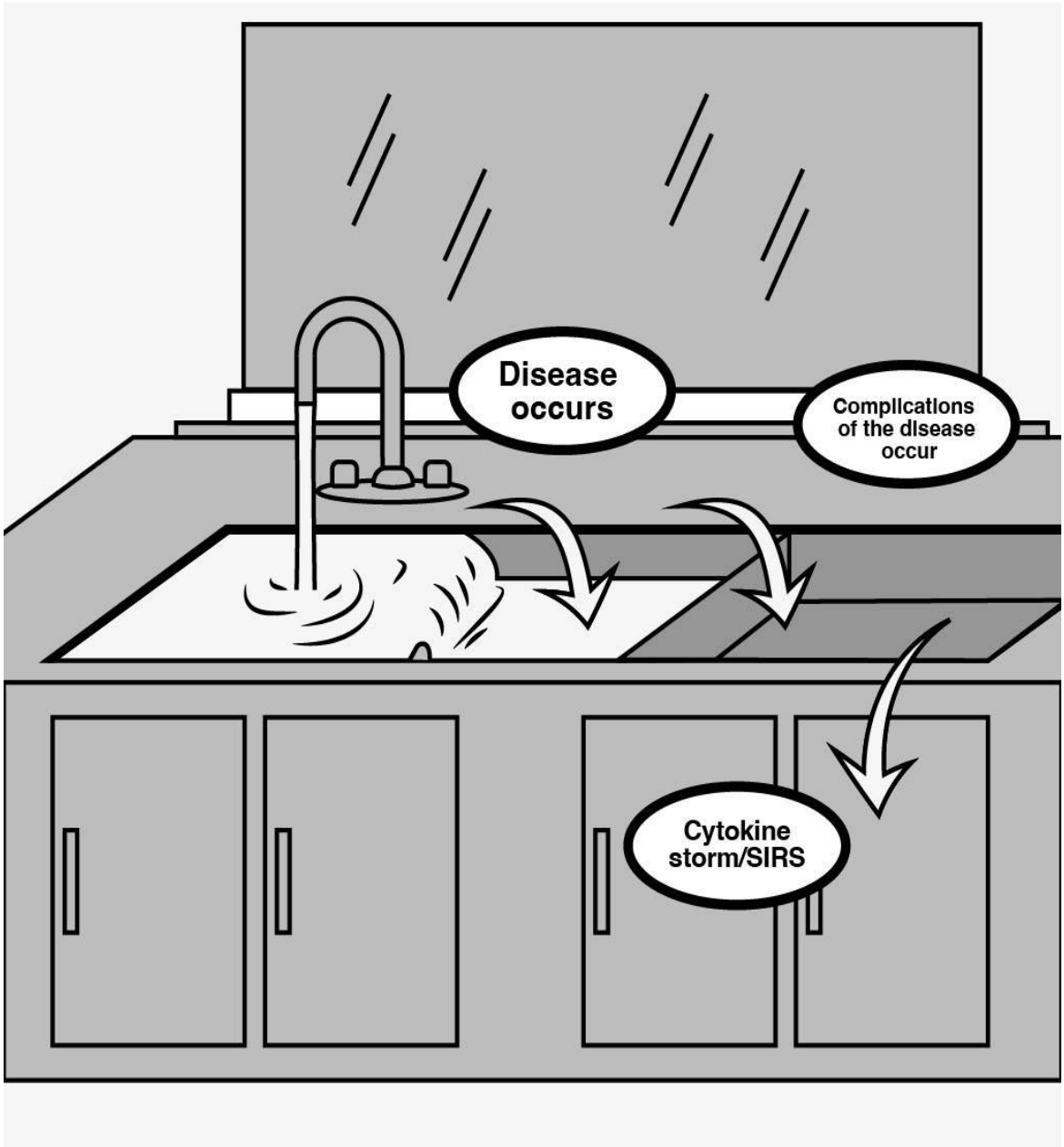

Figure 1. Triple oxidant sinks.

A similar situation occurs with surgical interventions. If the oxidant sinks are already partially full,due to chronic disease, cancer, or smoking, little reserve is seen before complications are induced. Complications could include infection, wound healing problems, joint stiffness, heterotopic ossification, venous thromboembolism (VTE), and many others. A study by Leimkuhler et al. states: "Our study shows that the surgery itself poses a direct burden on the antioxidant capacity of a patient… A depleted antioxidant capacity cannot counteract oxidative stress sufficiently and might leave the patient more prone to complications" [41].

Numerous studies have described the oxidative stress seen in sepsis and in other critically ill patients. Several papers imply that those that recover normalize their oxidative state where those that succumb do not recover their oxidative balance [42–44]. The oxidative sink analogy in relation to the trauma patient suggests pro-oxidants are tolerated until a threshold is reached. Once the oxidative stress threshold is surpassed, additional stressors cause complications. ARDS is not uncommon when pro-oxidants overwhelm the patient. If a damage control protocol is used allowing time to pass before further oxidative insults, the oxidant sinks empty from the ARE induced increased antioxidant production. The partially emptied antioxidant sink allows for further pro-oxidant generation with fewer inflammation-induced problems.

The oxidant sink theory may explain why there are some patients, exhibiting the very same injury pattern, who can survive trauma without severe problems, while others develop ARDS, and worse. The injury occurs, generating pro-oxidants in all comers [45]. Those with an adequate antioxidant capacity disarm the offending pro-oxidants preventing the trauma related conditions. If the oxidant sinks are closer to full, the same oxidant load results in complications.

Predisposing stressors and morbidity dramatically affects the ability to tolerate oxidative stress. Increased age is heavily associated with increased baseline oxidative stress [46] The elderly also have increased rates of trauma complications and higher mortality rates [47], indirectly supporting the oxidant sink theory. Another group of individuals with relatively full oxidant sinks are cigarette smokers. Cigarette smoking is highly pro-oxidant [10] and smokers have significantly worse trauma outcomes [48]. Patients with comorbidities associated with relatively full oxidative sinks including COPD, heart disease, and diabetes have worse trauma outcomes [49–51].

3. Sources of Oxidative Stress in Trauma

With current improvements in trauma care, survival rates have improved. As more severely injured trauma patients survive, elevated levels of inflammation are seen. Late deaths from multiorgan dysfunction syndrome and sepsis are a sequelae of that heightened inflammatory state. The inflammation generating mechanisms are complex, interconnected, and involve constituents of a number of different pathways. These are depicted in Figure 2 and summarize the rest of this section.

In severe trauma, ischemia-reperfusion (IR) is common from hypotension and reperfusion after resuscitation. During the ischemic phase, adenosine triphosphate (ATP) production is lacking to maintain cellular energy balance. Extracellular acidosis, lactate production, and intracellular electrolyte imbalance (especially intracellular calcium [Ca^{2+}] increase) leading to massive ROS generation by mitochondrial depolarization. Inflammatory cells are attracted by the cytokines produced (IL-1β, IL-8, and others). On arrival the inflammatory cells dump their pro-oxidant contents as well as other free radicals from the NADP+ cycle ("oxygen burst"). This cycle is potentiated with more cytokine production and immune cell recruitment via NLRP3 inflammasome upregulation [52]. The ROS oxidize the cell membranes and increase the leakiness of the cell and the mitochondria. The mitochondrial and DNA damage often lead to cellular apoptosis through a variety of mechanisms involving release of cytochrome C from the mitochondria, resulting in activation of JNK, p38 MAPK, or ERK1/ERK2 [53].

Severe soft tissue and bony injuries add further inflammatory cytokines [54]. Endothelial integrity is disrupted by tight and adherens junction oxidative injury [55] Fluid and inflammatory cells leak out of the vasculature, increasing local oxidative state. Systemic inflammatory response can follow from the release of the interleukins and complement activation [54]. The host is set up for a severe inflammatory hit that only heightens with time.

Small intestinal IR induces not only vascular, but intestinal wall permeability from mucosal injury with bacteria infiltrating the lining cells. Toll like receptor (TLR) 2 and 4 recognize these bacteria. Further leukocytes (especially neutrophils) are recruited. TLR-2 produces increases in NfκB and then TNF-α. TNF-α is thought to be the generator of ARDS and MODS from gut IR. The gut microbiome appears to mediate this enteral IR response [56].

Along with the endothelial permeability response to IR, cellular adhesion molecules (CAMS) promote neutrophil and other leukocyte translocation, further increasing the pro-oxidant environment. The predominating superoxide free radical reacts with nitric oxide producing peroxynitrite, inhibiting vascular relaxation [57].

Figure 2. Demonstrates a portion of the complexity of the trauma oxidative stress pathways leading to complications in black. It highlights the unlikely ability of single cytokine blockers to significantly alter the inflammatory cascade. Red reveals the multiple sites affected by whole plant antioxidants and fiber. IR—ischemia reperfusion; MCP-1—also known as CCL2, monocyte chemotactic protein-1; TNF-α—tumor necrosis factor alpha; TLR 2 & 4—toll like receptors 2 & 4; IFN-γ—interferon gamma; Nrf-2—nuclear factor erythroid 2-related factor 2; HGMB-1—high mobility group box 1; CAM—cellular adhesion molecule; SCFAs—short chain fatty acids, NF-κB—Nuclear factor kappa-light-chain-enhancer of activated B cells; PPARγ—peroxisome proliferator-activated receptor gamma; PUFA—polyunsaturated fatty acid; DHEA—dehydroepiandrosterone; IL—interleukin; ROS—reactive oxygen species; RNS—reactive nitrogen species; ARDS—adult respiratory distress syndrome; MODS—multiple organ dysfunction syndrome; SIRS—systemic inflammatory response syndrome; DAMPs—damage-associated molecular patterns; NLR—nod like receptors; PRR—pattern recognition receptor; STING—stimulator of interferon genes; IKK—inhibitory-kB kinase; NADP—nicotinamide adenine dinucleotide phosphate; JNK—c-jun N-terminal kinase, (MAPK family); MAPK—mitogen-activated protein kinase; ERK ½—extracellular signal-regulated kinases 1 and 2; WBC—white blood cell.

The highly concentrated mast cells (10^4–10^6 mast cells/gm connective tissue) are partially responsible for soft tissue inflammation as injured/necrotic cells release "alarmins" or damage-associated molecular patterns (DAMPS) initiating the inflammatory response. IL-33 is one alarmin recognized by nearby mast cells [13]. Sensitized mast cells are further stimulated by ROS which stimulate the Ca^{2+} dependent mast cell degranulation producing cytokines, leukotrienes, and prostaglandins [58].

Trauma induced endothelial injury activates platelets. Additional platelets and leukocytes are recruited, further escalating oxidative stress and creating a vicious inflammatory cycle [54].

Cellular injury produces release of mitochondrial and/or nuclear DNA. These stimulate other DAMPS through pattern recognizing receptors (PRR). Inflammasome formation is induced and pro-interleukin 1β (IL-1β) and pro-IL-18 are formed from induced protease caspase-1 activity. The cascade towards SIRS is potentiated [59].

The PRR also stimulates the protein stimulator of interferon genes (STING) resulting in phosphorylation of IKK and then blocking the inhibitors of NfKb, inducing increasing inflammatory cytokine production. STING stimulation also upregulates the production of type 1 IFNs [59].

DAMPS from multiple sources, produced during trauma and the post-trauma inflammation, are recognized by nod like receptors (NLR) causing production of inflammasomes which activate caspase. Activated caspases induce release of IL-1β and IL-18 and can trigger a proinflammatory cell death termed pyroptosis. IL-1β, a major force in the inflammatory cascade, induces IL-6, IL-8, MCP-1, IL-1α and β, platelet activating factor, and eicosanoid production. IL1-β also stimulates increased cellular adhesion molecules and chemoattractants increasing leukocyte recruitment and translocation. IL-18 also promotes expression of CAMS, production of inflammatory cytokines and chemokines, and stimulates IFNγ. Platelets are activated and further inflammatory contents are released including IL-1β and others, with continued amping up of the inflammatory cascade.Transfusions, while necessary, can also contribute to this cascade due to cellular lysis resulting in increased DAMPS from the cellular debris, additionally promoting inflammasome formation and inflammation potentiation from other pathways [59].

The immune response is closely linked to progression of traumatic brain injury (TBI) through inflammasomes NLRP1 and NLRP3 worsen results after TBI. TBI results are improved with the downregulation of both NLRP1 and NLRP3. Acute lung injury is tied to inflammasome dependent excessive inflammation and then to ARDS. Dampening of the NLRP3 response decreases ARDS and improves lung physiology. Inflammasomes are also heavily associated with the development MODS [59].

The inflammatory state inhibits the immune system in preventing bacterial growth with infection and sepsis frequently resulting. The post-trauma immune suppression is partially credited to suppression of macrophage and monocyte function by inflammasomes. Infection and sepsis only further compound the organism's oxidative state [59].

Neuroendocrine hormonal changes occur during trauma. Cortisol, strongly anti-inflammatory, is released causing lymphocyte apoptosis and inhibiting the innate and adaptive arms of the immune system. Neutrophil release is also stimulated, including the marginated population. Dehydroepiandrosterone (DHEA) is produced from the hypothalamic-pituitary axis activation. Due to the trauma, DHEA is reduced and the cortisol:DHEA ratio is very elevated, increasing infection risks [54].

The neutrophil is the most sinister actor in the response of the body to trauma. There is a characteristic increase in the neutrophil to lymphocyte ratio (NLR) seen in trauma, a hallmark of oxidative stress. Increased mortality rates are seen with NLR alteration outside of trauma including oxidative stress associated cancer, medical problems, and even COVID-19 [60,61]. In trauma ICU patients, and especially TBI patients, an elevated NLR is an independent risk factor for complications and mortality [62]. Multiple pathways lead to neutrophil recruitment with cells of all ages mobilized. As the increasing number of recruited neutrophils mount, more immature neutrophils are called up. Sensitized neutrophils, when exposed to IL-1β (in vitro) and IL-8 and lipopolysaccharide (LPS) (in vivo), expel their DNA creating a net (neutrophil netosis). The DNA histones lose their charges with the interactions with the free radicals and the DNA is then unwrapped and extruded out of the cell wall possibly causing more DAMPs, compounding the inflammatory insult [63].

4. Oxidative Stress Induced Problems in Trauma

ARDS and MODS, as mentioned above, have a high association with severe trauma and very high oxidative stress [59]. Predictive cytokine alterations have been found to include: IL-6 is associated with multi-organ dysfunction syndrome, multi-organ failure (MOF) and mortality. IL-8 alterations are seen in ARDS, MOF and mortality. IL-10 changes may be seen preceding sepsis and MOF, while TNF-α may be related to MOF [42].

Trauma induced coagulopathy has been shown to be directly associated with oxidative stress. Post translational fibrinogen is altered by free radicals, changing its structure which inhibits polymerization of fibrinogen. A less stable clot is formed, more susceptible to fibrinolysis [64]. Platelet hypoactivity can also be seen in oxidative stress, potentiating coagulopathy [65]. Though platelet hypoactivity can occur with RNS, more commonly hyperactivity of platelets occurs from ROS leading to hypercoagulability and subsequent venous thrombo-embolic disease [65]. Hypercoagulability is also seen with the lack of superoxide dismutase (SOD) initiating methionine oxidation of thrombomodulin dramatically decreasing thrombomodulin-dependent activation of protein C [66]. Oxidative stress also induces CAM potentiating the aggregation of the activated platelets further promoting VTE.

Endothelial intercellular integrity is altered in redox imbalance causing (1) tight junction injury; (2) tight junction controlling protein changes, also increasing leakiness; (3) occludin down regulation further compromising tight junction integrity; (4) phosphorylation induced adherens junction disassembly; (5) ROS induced increased Ca^{2+} cellular concentration activating actin, changing cellular shape further increasing leakiness [55]. These changes add to the generalized swelling seen in multi-trauma patients.

Abdominal and extremity compartment syndromes result from multiple oxidative stress pathways. IR produces an increase in the local pro-oxidant cytokines. Disruptions of the tight and adherens junctions lead to further local swelling. Characteristic outflow occlusion results with attendant compartment syndrome [67–70].

The brain is thought to be the organ most susceptible to oxidative damage due to high glucose and oxygen use [71]. Unsaturated and polyunsaturated fats are in abundance and are at high risk for oxidation by free radicals and lipid peroxidation. The initial trauma invokes the first hit with the secondary oxidative stress inducing further neuroinflammation. Brain edema results from mitochondrial disruption, blood brain barrier disintegrity, endothelial damage and leakage, and secondary neuronal injury [72]. With blood brain barrier disruption, the brain is exposed to systemic oxidative stress and further damage. CAMs expression leads to potentiated neutrophil migration into the brain, further intensifying the pro-oxidant environment. ROS from the injury contributes to neuroinflammation with possible resulting cognitive, emotional and behavioral problems. The elderly are particularly affected with decreased neuroplasticity and cognitive decline with hippocampal involvement [54].

Subjective aging after significant trauma has been reported by patients. This is not surprising as the mitochondrial theory of aging suggests that ongoing cumulative oxidative stress promotes not only disease states but also premature aging [4,66]. The triple oxidant sink theory would also predict a loss in the vital force of individuals after severe trauma. This could be from sarcopenia and dynapenia mentioned above as well as just a manifestation of accelerated aging from the oxidant stress.

Hypoalbuminemia has been a particular concern in the multiply traumatized individuals. Generalized body swelling has been blamed on the albumin induced vascular osmotic pressure loss. Though this may contribute, endothelial permeability from free radical injury to cellular attachments is also a vital factor (as noted above). Albumin is a preeminent free radical scavenger due to its abundance and free thiol groups. The rapid depletion of the albumin is a marker of oxidative stress/inflammation [73].

In addition to blood loss related anemia in trauma patients, oxidative stress has been shown to decrease the life of RBCs (eryptosis) and and can suppress hematopoietic precursors, further reducing oxygen transport capacity [74,75]. Thus transfusions are often required, further filling the oxidant sink through DAMPs.

The literature abounds with additional negative outcomes that are attributable to trauma and oxidative stress, occurring acutely, sub-acutely and even more chronically, including: post-traumatic stress disorder [76], fracture nonunion from osteoprogenitor cell inhibition [77], wound healing problems [78], infection [79], heterotopic bone formation and stiffness [80], post-traumatic arthritis [81,82], chronic regional pain syndrome-1 (CRPS-1) [83,84], delirium in the elderly [85,86], hyperglycemia [87], and more.

5. Potential Solutions?

Oxidative stress is, by definition, a relative lack of antioxidants in relation to pro-oxidants. With a lack of antioxidants, antioxidant supplements could be considered. Unfortunately, studies have shown that antioxidant supplements have been, at best, minimally helpful and, at worst, harmful in humans [88–90]. The 2023 NIH statement on antioxidant supplements does not support their use [91]. Trials of vitamin E in patients with heart disease and cancer risks found no improvement in rates of MI, stroke, or cancer and had a higher risk of heart failure than those not taking vitamin E supplements [92]. Antioxidant supplementation in the ICU has been equally disappointing, making some even question the theory of oxidative stress and antioxidants [93,94]. (See Table 1).

Table 1. Antioxidant supplement studies.

Participants	Intervention	Comparison	Outcome	Study Design
High grade prostate intraepithelial neoplasia and/or atypical small acinar proliferation.	Lycopene, selenium, and green tea catecholamines vs. placebo	between groups	Prostate cancer (Pca) incidence 3X in supplemented group and miRNA implicated P ca progression, chemo promotion not chemo prevention [95]	Randomized, double blind, placebo controlled
multiple studies	vitamin E supplements	between studies	vitamin E dose > 400 IU/day increased risk of all cause mortality [96]	Meta-analysis
High risk cardiovascular patients	ER niacin 2 gm with laropiprant 40 mg/day plus simvastatin vs. placebo with simvastatin	between groups	study stopped prematurely due to myopathy in treated patients [97]	Randomized, placebo controlled
Atherosclerotic heart disease	ER niacin 1500–2000 mg/day plus simvastatin vs. placebo plus simvastatin	between groups	no clinical benefit adding niacin [98]	Randomized, placebo controlled
Cardiovascular disease prevention and treatment	Vitamins and mineral supplements	between studies	"Conclusive evidence for the benefit of any supplement across all dietary backgrounds (including deficiency and sufficiency) was not demonstrated." [99]	Meta-analysis
>20 yr old adults	Observational	Dietary supplement and nutritional intake from foods and supplements	Dietary supplements not associated with mortality benefits in US adults. Adequate nutrient intake was associated with reduced all-cause or CVD mortality, but the associations were confined to nutrient intake from foods and not supplements [100].	Cohort study
Healthy volunteers	Vitamin C 500 mg/kg X 6 weeks	Lymphocyte DNA damage before and after intervention	Increased lymphocyte DNA damage with vitamin C [101]	Intervention trial
Critically ill adults	Glutamine, antioxidants, both, and placebo	Between groups	No improvement with antioxidants, increased mortality in glutamine group with association towards multiorgan failure [102].	Blinded 2X2 factorial trial
Critically ill adults	Antioxidant micronutrient supplementation	Between studies [103]	Evidence does not justify administration of antioxidant micronutrients to critically ill patients.	Systematic review with meta-analysis and trial sequential analysis of randomized controlled trials.

There has been a renewed interest in antioxidant supplementation in ICU and trauma patients due to the massive potential gain with redox balancing. Unfortunately, recent results have also been mixed and relatively disappointing. Rather than supplementing with an isolated antioxidant, could supplementing with high antioxidant whole plant foods, which has been successful in chronic oxidative stress be effective [104–106]?

There is an apparent synergy between the antioxidants contained within each whole plant and the isolated antioxidant may not fulfill its characteristic role without its synergistic partners [107–109]. While whole plant derived antioxidants have been shown to be effective in treating chronic oxidative stress, they have not been used to treat acute oxidative stress.

Current protocols for feeding ICU patients are based on calculated caloric requirements and nitrogen balance. Though the feeding protocols do have historic value in trying to optimize patient nutrition, questions arise as to their current value. The impact of the immune response to burn and injury has the major influence in morbidity and mortality and should, if possible, be addressed, at least partially, with nutrition. Also, it appears that energy production in the face of mitochondrial dysfunction is very altered and may be exacerbated by increased caloric intake [110,111], especially in the form of processed foods without antioxidants and fiber. From the research literature, the nitrogen balance problem appears to be due to free radical and pro-oxidant "injury" to proteins (especially albumin) [28,112,113], in these patients with oxidative stress. As the protein structure is altered from the injury, altered function and 3D structure is changed, and the proteins are recycled.

From a mere theoretical point of view, the knowledge that consumption of highly processed foods contribute to poor health has trickled into the lay literature. Elemental diets may be some of the most highly processed foods, eliminating antioxidants and fiber critical for free radical scavenging and redox balancing.

5.1. Reasons Why Using Whole Plant Foods as Medicine Could Be Useful

(1) Whole plant antioxidants and fiber along with other lifestyle modifications have been successful in treating chronic oxidative stress [104,114].

(2) Spices have been shown to have free radical scavenging ability (very high ORAC values), immunomodulatory effects, and the ability to improve the health of the gut microbiome [29,115–117].

(3) Spice induced gut microbiome optimization occurs via killing of the pathogenic gut bacteria and stimulating growth of the beneficial bacteria almost like a probiotic [117].

(4) Sulforaphanes, from cruciferous vegetables, are thought to be one of the most potent immunomodulators and have been shown to have multiple effects: (A) Sulforaphanes have been thought to be one of the most potent activators of Nrf2-mediated phase II enzymes. Upregulating Nrf2 induces the antioxidant response element DNA sequence transcription, encoding for increased endogenous antioxidant enzymes. (Nrf2 has been shown to be protective for the lung against oxidative stress) [118–120]. (B) Sulforaphanes down regulate Nf_KB which is responsible for the production of the oxidative stress cytokines [32]. (C) Sulforaphanes upregulate glutathione production (endogenous non-enzymatic antioxidant) [121]. (D) Sulforaphanes increase heat shock responses further promoting cell stability [122]. (E) Sulforaphanes decrease secretory leukocyte protease inhibitor which inhibits proteases like cathepsin G and neutrophil elastase which are both associated with lung damage [118].

(5) Extremely important phytonutrients including: phenolic acids, flavonoids, tannins, carotenoids, etc., have multiple beneficial effects. Free radical scavenging, immunomodulation suppressing many different inflammatory pathways, and upregulation of anti-inflammatory pathways are noted with their consumption [123].

(6) Fiber from whole plant foods boosts short chain fatty acid formation in a healthy gut microbiome leading to oxidative stress immunomodulation [124].

(7) In one meta-analysis it was found that increased fiber consumption and the C reactive protein were inversely proportional [125]. C-reactive protein is highly correlated with acute oxidative stress complications in COVID-19 patients [126].

(8) Butyrate has been shown to decrease TNF-α mediated immune responses and mitochondria derived inflammasomes such as NLRP3 [127].

(9) Short chain fatty acids regulate MAPK pathways and inhibit activation of proinflammatory ERK, JNK and P38 MAPK pathways [124].

(10) Gut inflammation and leakiness is subdued with stimulated TGF-β, IL-10, and IL-18 [128].

(11) Butyrate has also been shown to have an anti-inflammatory effect on the bone marrow derived macrophages strongly decreasing IL-6, TNFα, IL-1β, and inducible nitric oxide synthase and increasing IL-10 [129].

(12) Mitochondrial induced oxidative stress is decreased through the communication with a healthy gut microbiome [130].

(13) Many of the inflammatory cytokines and stress molecules (TNFα, IL-6, HIF, HMGB1, etc.) are inhibited by whole plant antioxidants [123,131,132] and fiber [127,133].

(14) Peroxisome proliferator activated receptor gamma (PPARgamma), an important constituent of the antioxidant defense system and an optimizer of mitochondrial function, is stimulated through SCFAs and ferulic acid [33,134].

(15) Clinical trials using omega-3 polyunsaturated fatty acid supplementation have had mixed results at best. Yet in vitro and animal studies suggest that the risks of ARDS and other pulmonary complications can be decreased, possibly through suppression of IL-6, TNF-α, IL-1β, and IL-8 and possibly other pro-inflammatory cytokines or to the reduced levels of PMNs recruited to the lungs [135]. Administering these omega-3s through whole plants may reap the results seen in the in vitro and animal studies.

(16) Vitamin D is known to dampen the inflammatory response through many mechanisms of improving oxidative stress. Mitochondrial respiration is stabilized (a significant source of free radicals), Nrf-2 is enhanced and NfκB is down regulated, along with a number of other immunomodulatory pathways decreasing oxidative stress [23]. Recent reports on acute oxidative stress in COVID-19 patients show that those with lower vitamin D levels have worse results [136].

(17) Vitamin B12 is thought to be a free radical scavenger and a glutathione preserver, another free radical scavenger. Immunomodulation is induced. Oxidative stress from homocysteine accumulation and from advanced glycation endproducts is mitigated [31].

(18) Antioxidants have been shown to stabilize the mast cells decreasing degranulation as well as production of many of the inflammatory cytokines [58].

(19) The effect of spices on oxidative stress is well described in a study by Oh et al. In this work IL-1β secretion from LPS-stimulated peripheral blood mononuclear cells (PBMCs) was significantly reduced—1314%—within approximately four hours after consumption of a high-saturated-fat, high-carbohydrate meal containing 6 g of spices. Let us emphasize this result, this is a 13× *decrease* in IL-1β, the upstream generator of multiple inflammatory cytokines, from addition of spice alone [137].

(20) Burmeister, et al., found that all deaths in trauma patients in their study were associated with the same profile of pathogenic gut microbiome organisms. On admission, fecal cultures were collected from all of the trauma patients shortly after arrival. All deaths were in the worst microbiome quartile, though not all in that lowest quartile died. Higher complication incidence was also noted. The authors suggest early microbiome changes could be life-saving [138].

(21) Cellular adhesion molecules can be decreased with a low fat, high antioxidant diet and butyrate [133,139,140].

(22) Free radical production by IL-1β, TNF-α, and IFN-gamma can be eliminated with antioxidants [141].

(23) Antioxidants can inhibit and reverse oxidative stress induced changes in tight and adherens junctions [140].

(24) and more.

Thus development of a protocol of feeding trauma patients whole plant based foods, selected for their antioxidants and fiber containing characteristics, that will replace current protocols utilizing highly processed foods that have been stripped of fiber and natural antioxidants, could potentially improve outcomes in this vulnerable patient population.

5.2. Multimodal Treatment of Acute Oxidative Stress May Be Indicated

Successful and conclusive application of the scientific method requires isolating different factors and randomly controlling variables to minimize confounders. However, in a problem as interconnected as acute oxidative stress, changing any one of the above-mentioned variables, as in TNFα, may not be sufficient to reverse the already progressing pathology. While Figure 1 is not a comprehensive summary of all pathways leading to inflammation, it provides a hint at the relative complexity and interconnectedness of multiple avenues to inflammation. Just blocking the effects of IL-6 or TNF-α with administration of a selective antibody is unlikely to stem the vast tide of inflammation. A strategic mix of the optimum benefits from many of the facets of the antioxidant shield may be needed to conquer a foe as formidable as acute oxidative stress.

Isolated interventions in acute oxidative stress may be helpful but may not be adequate to change the course of the disease. An example of that would be the spice study quoted above. Six grams of spice made a dramatic (13×) improvement in the IL-1β levels whereas those that had the 2 gms of the spices had no detectable clinical response. It is likely the addition of the 2 gms of the spices was helpful, but was not adequate. With oxidative stress, isolated, limited attempts at conquering it will likely be helpful but may not be adequate. An optimal,

strategic combination of the different free radical scavengers, immunomodulators, antioxidant response element stimulators, gut microbiome modifiers, and lung protective whole plant antioxidants theoretically would be most effective in stemming the tide of oxidative stress induced inflammation.

5.3. What If?

If we could change only one of the many resultant pathophysiologies caused by acute oxidative stress, it would have a dramatic impact on so many people around the world. What if we could affect *all* of the oxidative stress associated problems? What if TBI recovery could be enhanced? What if VTE, chronic pain, and PTSD could be eliminated? What if hypocoagulability, ARDS, and MODS could be prevented or reversed if experienced? What if damage control could be shortened or eliminated and acute total care could be accomplished? What if the massive swelling and the abdominal and extremity compartment syndromes could be prevented? Could rapid loss of muscle mass and strength be changed? Combined with the myriad of advances in trauma care over the past several decades, this non-pharmaceutical, nutrition-based intervention could revolutionize the medical response, improving outcomes in patients with injuries from relatively minor to severe.

This review is aimed at stimulating thought and research to treat acute oxidative stress which will spill over into sepsis and other ICU care. It is recognized that many of the concepts and assertions presented are based on a limited number of studies. Further validation of the concepts, assertions, and hypotheses will need to be established with continued scientifically sound research.

6. Conclusions

It is our hypothesis that acute, trauma induced oxidative stress could be mitigated using whole plant antioxidants and fiber as medicine, improving survival, function, and other outcomes while decreasing costs of trauma care. Food can and likely should be used as medicine, even for those in acute oxidative stress.

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