High fructose consumption: more pain than gain to human health

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Abstract

An imbalance in any metabolic system can be traced to its homeostasis. When homeostatic environment is not attainable then there will be a response from the body. A new shift has emerged, "the negative feedback effect of high fructose consumption;" more pain than gain. The human metabolic system daily combat fructose sugar metabolism which emanates from high consumption. This inadvently lead to a chronological series of complications arising from the feedback. These feedbacks play pivotal roles in skeletal muscle damage and other body frameworks, it also fosters toxic advanced glycation end products (AGEs), factors that impose and inflict damaging effects to the body`s energy currency and serious threat to health. These damages are missed or overlooked because of early nonspecific physiological symptoms. High level of fructose has both long- and short-term effects on human metabolic processes. These effects which are majorly through the production of reactive oxygen species (ROS) and other free radicals, are felt in the disruption of biomolecules such as causing DNA mutation, lipid peroxidation etc. these effects in turn lead to various diseases such as cancer, diabetes, atherosclerosis, and other health issues. In this review, we will focus on the damaging effects this sugar has on human health and the present solutions being applied. We will also look at the next step in combatting and controlling these negative feedbacks.

Keywords: Antioxidants, Free radicals, Fructose, Oxidative stress

Introduction

The exasperate negative feedback mechanism has been linked to an increased risk of a broad range of chronic metabolic diseases. Namely, cardiovascular disease, diabetes, dyslipidaemia, obesity, hyperglycaemia, high triglyceride centred on the concept "you are what you eat." How about the industrialized sweeten dairy contribution to this feedback loop with its negative outcomes in society, thus producing a considerable economic and medical burden on our healthcare system, existing literature highlights that dysfunctional insulin, liver due to excessive fructose ingestion has detrimental outcome linked to depleted ATP, metabolic syndrome, non-alcoholic fatty liver disease etc. All this research centred on the immediate manifestation

What of its long-term effects on metabolic system that is synonymous with a slow, gradual progression into oxidative stress, free radicals' generation that exact consequence on basic molecules such as DNA, lipids, and proteins which are the building blocks that aid longevity of life span; aids chronic inflammation and causes oxidative modifications of enzymes, lipid peroxidation. Thus, deterioration of the antioxidant defense mechanism altars redox regulation. These are critical for cell viability. Elucidating the effects in the future and continues to be an important handicap in resource-poor countries. In this review, we discussed the future outcome, potentiating high fructose ingestion on metabolic system of the body

High fructose diet is deleterious to the human metabolic system. This is a major concern as most of the metabolic health problems have been associated with high fructose consumption. Diseases such as cardiovascular disease, diabetes, dyslipidaemia, obesity, hyperglycaemia, and high triglyceride [1, 2] have all been mentioned. Its high consumption has risen since it is used as sweetener in most packaged diets. High fructose diet intake has been shown to alter cellular and molecular metabolic processes within the cell resulting in severe deleterious effect in the life span of an individual [3]. However, the behaviour of human beings and the industrialised world in modifying the human diet with sweetened power to prolong shelf life of food has played vital role in the ingestion of high fructose diets as well as the prevalence of metabolic abnormalities [4, 5].

Oxidative stress can be defined as the inability of the body cell to balance or maintain homeostasis due to low antioxidant capacity leading to high degree accumulation of reactive oxygen species (ROS) [6]. This leads to oxidative damage thereby altering the mitochondrial bioenergetics and degradation of the body system [7]. Oxidative stress causes damage to cellular functions and it linked to several abnormalities within the cell such as cancer, diabetes as well as cardiovascular diseases.

Skeletal muscle is one of the vital and most dynamic plastic tissues in the body system. It plays a significant role and contribute to most of the body functions. In terms of metabolic processes, it serves as storage of basic important macro molecules such as protein, lipids and glucose [8]. skeletal muscles have been found to be a major

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factor to be considered when it comes to the control of glycaemia and metabolic homeostasis [9]. It is the predominant site for glucose disposal in insulin mediated conditions. Along with the liver, skeletal muscle stores glycogen. It has four fold capacity more than the liver making it the highest glycogen reservoir in the body [10].

Antioxidant enzymes are known to maintain stability and control the increase of free radicals caused via the action of oxidative stress in the body [6]. Because of their potential harmful effects, excessive ROS must be promptly neutralized and eliminated from the cells by a variety of antioxidant defence mechanisms. Oleanolic acid is a natural triterpenoid of many saponins which aid the improvement of insulin response and preserve beta cells [11]. According to Wang, Li, Wu, Liu, Hu, Liao, Peng, Cao, Liang and Hai [12], oleanolic acid has been shown to have protective effect against certain hepatotoxicants such as acetaminophen that cause oxidative and electrophilic stress. Studies have shown that oleanolic acid contains antioxidant activity and thus can lower hyperglycaemia effectively as well as serving to ameliorate high fat diet in visceral obese mice [13]. This review discusses the effect of prolonged consumption of high fructose sugar and the need for supplementation to boost the system defence mechanism and cell longevity.

High fructose consumption

Fructose is a monosaccharide present in many fruits class and honey. Although, its chemical formula with that of glucose ($C_6H_{12}O_6$) is the same, the only difference in their structures is that fructose has five atom rings with the second carbon atom having a keto group (a non-reducing sugar) that is attached to it, while glucose is made up of six atom rings with the first carbon having an aldehyde group (reducing sugar) attached to it (figure 1). These sugars are both reducing sugars. While glucose is the main energy source for most part of the body especially the brain, fructose cannot enter most cells. Unlike glucose, it is mainly limited to the liver [14].

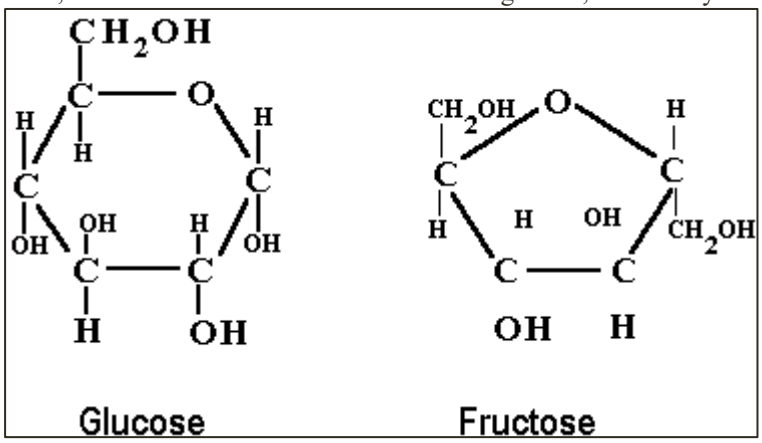

Figure 1 Chemical structure of glucose and fructose

Trend in fructose consumption

In 1960, high-fructose corn syrup (HFCS) was developed as a result of scientist invention of technologies that allow corn starch to be remolded into HFCS [15, 16]. This HFCS contains high fructose level, it is inexpensive and in acidic condition; it is stable in foods as well as in beverages. However, its consumption has increased and doubled between 1970 and 1990. HFCS contains 55% of free fructose with 42% of free glucose, while 3% portion of HFCS is for other sugars, this has significantly increased fructose consumption making a total tall of 85 to 100g per day [17]. Nowadays, HFCS is used in the manufacturing of processed foods as well as beverages in place of sucrose; these processed products include sodas, candies, drinks, juices, cereals, dairy products, and jams, among others. The increased usage of HFCS arises from its low cost, its high concentration of sweetness as well as its ability to improve the shelf life of products [17].

It has been postulated that high level of HFCS food can bring about increase in lipogenesis, high levels of plasma triacyclglycerols (TAGs), obesity and cardiovascular abnormalities [18]. When ingested in large amounts, fructose can cause hepatic insulin resistance, leptin resistance, accumulation of ectopic fat in the liver and skeletal muscle, with visceral fat mass accumulation as well as increase in total fat [19]. It is known that moderate amount of fructose does not have any negative effect, mainly because there is decrease in the response to glucose loads, as well as improving glucose tolerance [20].

Fructose metabolism

Fructose metabolism differs from that of glucose because in the initial metabolic step of fructose, a dissimilar enzyme and responses takes place; which is the enzyme fructokinase. Fructokinase catalysis the phosphorylation

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of fructose into fructose 1-phosphate as seen in the above (Figure 2). The fructose 1-phosphate is then taken up and metabolised in the liver where it is directed towards replenishment of liver glycogen and triglyceride synthesis. Thus, when the liver takes up ingested fructose, it may produce CO_2 after being oxidized and this can further lead to the production of glucose and lactate in the biological system when it is further converted. Both lactate and glucose produced are then either allowed or enable to escape into circulation for extrahepatic metabolism, or it is converted to fat and hepatic glycogen. The phosphorylation and enormous absorption of fructose within liver causes massive ATP to AMP as well as uric acid degradation [21-24]. Steady fructose ingestion prompts de novo lipogenesis, causes high level accumulation of hepatic fatty acids in the body, and can result to ectopic liver fat when stored or deposited due to lack of usage by the body system or it is secreted as VLDL-triacylglycerols. Also, fructose impairs the extrahepatic clearance of VLDL-triacylglycerol's. Consumption of large amount of fructose diet results to the depletion of ATP, hyper-triacylglycerolemia; thus stimulating visceral fat accumulation as well as leading to the deposition of ectopic lipid in skeletal muscle of the body [21, 25, 26].

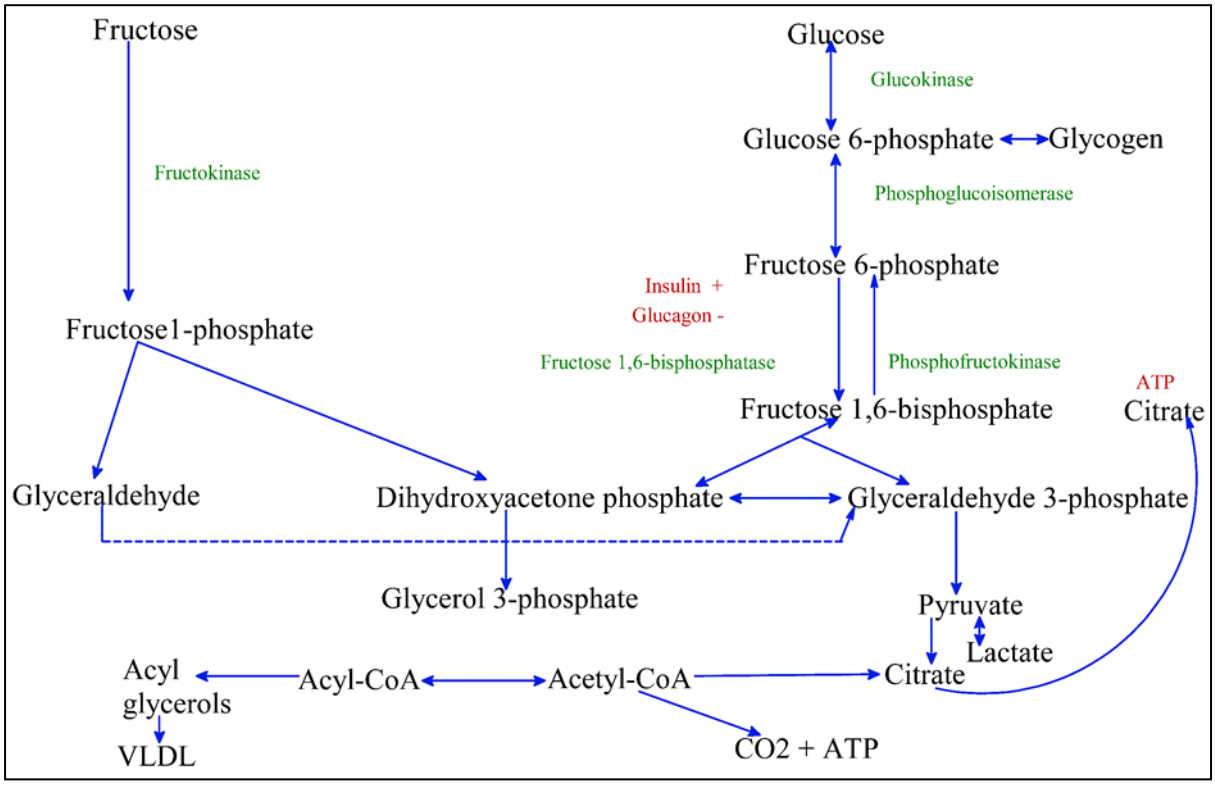

Figure 2 Metabolism of fructose and Glucose

High fructose Consumption and body complications

Fructose consumption at higher concentrations can also promote all the problems associated with complications known as metabolic syndrome. Metabolic syndrome is an abnormal clusters of risk conditions that correlate as a result of disrupted proper functions of the biochemical system of the body [27]. It is also known as syndrome X, insulin resistance syndrome, or multiple risk factor syndrome [28]. The classified risk conditions range from diabetes, hyperglycaemia, dyslipidaemia, cardiovascular diseases and obesity [29]. Diabetes is a disease condition characterised by a severe hyperglycaemia (increase in blood glucose level in the body system) due to either defects in insulin secretion or deficient action of insulin on target tissue [30]. On the other hand, dyslipidaemia is an abnormality of elevated lipoproteins such as serum triglyceride, apolipoprotein B, increase small LDL cholesterol, VLDL cholesterol, while obesity refers to a condition characterised by an unusual accumulation of excess storage fats in the body system [31].

Metabolic syndrome also causes cardiovascular diseases which generally refer to conditions that lead to either partial or total blockage of the blood vessels resulting to heart failure, stroke, chest pain and heart attack [32]. Globally, metabolic syndrome has recently increased with the rise in industrialised dietary foods. This has caused a challenge to public health because it is not age specific [33]. Fructose high ingestion can cause deleterious damage to the body metabolic system. Its low economical cost and availability have increased its usage than glucose in our industries today [34]. Different associations and international bodies have been trying to diagnose

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and find the reasons behind the sudden rise in the mortality rate caused by this syndrome, but there is no diagnostic measure specific to the syndrome [35]

Oxidative stress: feedback effect of fructose consumption

The consumption of dietary fructose which is known as sweetened foods is now prevalent in our society today. the behaviour of human beings and the industrialised world in modifying the human diet with sweetened power to prolong shelf life of food has played vital role in the ingestion of high fructose diets as well as the prevalence of metabolic abnormalities [4, 5]. According to Lai, Chandrasekera and Barnard [36], "what you eat" defines your metabolic state of health. The healthy state of an individual depends upon his/her nutritional behaviour. The upsurge of metabolic complications in humans has been linked to high consumption of carbohydrates and fat diets for the past decades in the western developed countries [37]. Fructose is a natural sugar which serves as dietary ingredient and has the tendency to cause rise in oxidative stress [3]. This oxidative stress is defined as the inability of the body system to maintain a constant balance between the generation of reactive oxygen species (free radicals) and scavenging of reactive oxygen species that result from various metabolic pathways [6]. These ROS have deleterious consequence on basic biological molecules which include DNA, lipids, and proteins which are the building blocks that aid longevity of life span [38]. The biological system suffers oxidative damage caused by lipid peroxidation due to the removal of electrons within the lipid membrane via the action of ROS [39]. ROS reaction also aids chronic inflammation and causes oxidative modifications of enzymes (proteins), the body's nucleic acids and deterioration of antioxidant defences mechanism which thus affect biological functions such as regulation of redox state, its proliferation and activation which are critical for cell viability [40-42]. Both oxidative stress and inflammation pathways are interconnected, owning to the fact that inflammation can induce oxidative stress and the production of free radicals is a characteristic property of activated immune cells which exacerbate this accumulation [43]. Skeletal muscle has shown a series of deterioration caused by oxidative stress reaction. During ageing it has been shown to result to cellular dysregulation [39].

Oxidative damage from free radicals

Free radicals are molecules that have one or more unattached electrons. The presence of these electrons makes the radicals become unstable, thereby inducing more reactivity in them. Production of free radicals by biological substances was first reported in 1954 [44]. These free radicals, which are toxic by-products of biochemical metabolic processes in the body that has cytotoxic damage to body cell and tissues, are made non-toxic by the antioxidant. Free radicals which induce deleterious effect in biological system comprise of superoxide radical, hydrogen peroxide, nitric oxide, hydroxyl radical, hydroperoxyl radical, hypochlorite ion, singlet oxygen but the most concern are collectively known as reactive oxygen species [38, 45].

Generally, the outer orbit of these molecules have an unpaired free shared electron which makes them very reactive and unstable [46]. In aerobic life the production of free radicals such as reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive chlorine species requires the availability of oxygen and are generated persistently via normal cellular metabolism in the biological system while some of these radicals are also induced by activated cytokines such as macrophages [6, 39, 45]. At increasingly accumulation; Reactive oxygen species are deleterious with a devastating consequence on cell membranes, including phospholipids, other major organelles which include lysosomes, mitochondria, DNA as well as nucleotides, it also aid in enzymes degradation as well as impede cell proliferation and migration [47]. In the cell, the main free radicals formed are superoxide (O_2^-.) that are produced via partial reduction of oxygen in electron transport system, and nitric oxide (NO) which is produced through enzymatic reactions

Superoxide's are oxygen derivatives and are produced via aerobic metabolism in the mitochondrial electron transport system since NADH, NADPH and $FADH_2$ are produced as a result of dietary intake thus, increases the release of free radical [45]. Furthermore, ROS are extremely reactive cytotoxic agent damaging cellular structure and cause dysregulation of the body metabolism by inducing deterioration in the form of lipid peroxidation, nuclei acid damage, oxidative modification of protein molecules [40, 48]. One of the amino acids in the muscle that is involved in cell division is glutamine. It is found in the blood and degraded to glutamate. The glutamate serves as a substrate for nucleotide biosynthesis, glucose synthesis or as fuel (ATP production) in the body. However, at elevated levels of free radicals in the biological system, it causes a drastic decrease in glutamine, thus influencing immune function and altering the availability of glutamine to leucocyte and result to low muscular performance [49, 50]. ROS play significant contribution in most of the human pathological disorder in patient with high risk of complication caused as a result of oxidative stress within body system [51]. Some of the vital ROS are recapitulating below in table 1.

Table 1 Free radicals and their effects in biological system

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Free radicals	Characteristics	References
Superoxide	Commonly produced as biochemical reactions intermediate that is impermeable to cell membranes and its negatively charged with hydroxyperoxyl radical being an exception. It has long half-life and can be produced by many cells when fighting against pathogens. Dismutation of hydrogen peroxide in the cells by superoxide dismutase helps to prevent damages within the biological system.	[52, 53]
Hydroxyl radicals	They are very reactive due to their strong oxidizing potential. They would normally cause damage to surrounding molecules. They are the most damaging ROS and can be said to be non-existing if not for the presence of some products of their reactions. They are not permeable.	[54, 55]
Singlet oxygen	Another essential ROS with limited half-life yet; permeable to cell membranes. It is oxygen in its excited state but without unpaired electrons so it cannot be termed as a radical. In water, the dismutation of superoxide anion brings about the production of high oxidizing singlet oxygen.	[56, 57]
Hyperchlorite	It is formed because of the activity of myeloperoxidase in the biological system using hydrogen peroxide. It is frequently created via the action of neutrophils also hazardous to thiols, ascorbate, lipids, and NADPH. In acidic form, it is permeable to cell membranes.	[58, 59]
Peroxynitrite	This is produced from the reaction between nitric oxide and superoxide. It is a fast reaction even more rapid in reaction than NO with a protein's heme. It is a strong oxidizing agent that can damage DNA, reduce thiol groups and subsequently cause protein damage.	[60, 61]

Skeletal muscle: roles and functions in the body

The origin for the build-up and regulation of force for locomotion is provided by the skeletal muscle [62]. They support the body in many ways such as maintenance of posture; they produce movement that influences activity. They are a storage for important substrates such as amino acids and glucose carrying the whole-body weight in all the different postures like standing and sitting, as well as being the focal point when an organism is in motion. The skeletal muscle can be said to be the main muscle that the body rely on. It is very relevant when it comes to posture and every other activity that involves movement of the organism. It majorly connects with the bone to carry out its functions [63]. Skeletal muscle comprises of some well-defined units that are attached to the bones or other muscles through the tendon and ligaments respectively which help in supporting special locomotion processes. It is heterogeneous and contains both light chain and heavy type 1 and 2A, 2X such as myosin, tropomyosin, troponins and actins complexes [64]. It also comprises of most of the proteins of metabolism taking part in excitation-transcription coupling.

Skeletal muscle can adjust its size and function in response to internal and external feedbacks. About 630 muscles which make up 40% of the total body weight are found in humans and contained about 50-75% of all body protein as well as 5% of other substances which include fat, carbohydrates, minerals and inorganic salts [8, 65]. Apart from its function in locomotion, skeletal muscles have been found to be a major factor to be considered when it comes to the control of glycaemia and metabolic homeostasis [9]. It is the predominant site for glucose disposal in insulin mediated conditions. Along with the liver, skeletal muscle stores glycogen as it has four fold capacity more than the liver making it the highest glycogen reservoir in the body [10].

Skeletal muscle is different from other muscles in the sense that it is the single one of its kind that can sporadically cause an increase in its energy consumption level when there is need for sudden and volatile contractions. This energy increase level can rise to 300-fold from the resting state to the fully active state which takes just few milliseconds to occur as it is extremely fast [66]. This ability to speedily increase its rate of energy production and flow of blood which usually takes place in response to locomotion solely distinguishes the skeletal muscle from others. Movement or locomotion is caused by the sliding filament theory of the actin-myosin cross-bridge during the skeletal muscle contraction [67]. The energy in the cross-bridge is provided by the hydrolysis of adenosine triphosphate (ATP) with myosin ATPase being the enzyme involved [68]. In metabolism, changes occur due to different activities going on in the body. One of this changes is caused or induced by exercise and this type of change due to exercise is majorly carried out by the skeletal muscle [69]. During exercise, oxygen consumption

increases to about 30-fold as well as blood flow. TCA also increases to about 70 to 100 fold [70]. The energy used by the skeletal muscle which is in the form of ATP is gotten majorly from oxidative phosphorylation. This is made very possible and easy due to the high presence of mitochondria in the skeletal muscle [71]. For energy production from carbohydrate and lipid metabolism, skeletal muscle is the main site though its actions can be regulated by the actions of the contractile bioenergetics involved.

Effect of oxidative stress on skeletal muscle

Skeletal muscles are vital and most dynamic plastic tissues and constitute the largest insulin-sensitive tissue as well as being paramount in most of the body functions. The vulnerability of the body high ingestion of fructose causes oxidative stress in the skeletal muscles. Majority of researchers have shown that oxidative stress can be deleterious to cells and is a major cause of most chronic diseases known. Why is oxidative stress so detrimental and what causes it?

For more enlightenment, oxidative stress is the damage caused to cells, tissues, or organs by reactive oxygen species (ROS). ROS are produced from the free radicals which are present in cells. Although free radicals are regarded as deleterious, they have been found to be of help in the control of signaling pathway, control of gene expression and in the modulation of muscle force generation [72]. Alternatively, oxidative stress has been redefined as the macromolecular oxidative damage resulting from the disruption of redox signaling and control [73]. Simultaneously, other metabolic pathways are compromised due to the generation of ROS in the skeletal muscles [74, 75].

Myofibrils are affected by oxidative damage during prolonged exercise in skeletal muscles due to the effect of muscle contractions which produces free radicals [76]. Early event in apoptotic pathway triggered by ROS in oxidative stress program the death of mature skeletal muscle cell which also causes death of progenitor [77]. Owing to the necessity of maintaining a state of normality in cells, antioxidant defense mechanisms are available in cells including skeletal muscle fibers in order to suppress damages due to oxidative stress as a result of the production of ROS [78].

Skeletal muscle and effect of antioxidants

Antioxidants maintain a balanced physiological ROS levels where they can function in signal transmissions [79]. Antioxidants serve to prevent oxidation. These antioxidants are well organized and function effectively to prevent the generation of free radicals [80]. These antioxidant enzymes affect the maturation of skeletal muscle cell and tissues regeneration [81]. Endurance exercise induces passive oxidant agitation in skeletal muscles, resulting in the oxidative capacity of skeletal muscles, its endogenous antioxidant enzymes and insulin sensitivity [82]. This supports the findings in the hormesis hypothesis in the sense that adaptations through exercise occur by the activation of signaling pathways leading to increased production of antioxidants [83]

According to Silvestre, Smadja and Lévy [84], the significant function of antioxidant defense enzymes in the development of new blood vessels (angiogenesis) and regeneration of muscle are interconnected in which the induction of angiogenic response which occurs as a result of the disruption of oxygen supply in a study of hind limb ischemia model that was carried out. Both angiogenesis and fibrosis are not considered as part of the restoration of skeletal muscle constituent, but the events are actually correlated. When vast muscle progenitor cells are restricted closer to blood vessels, the muscle becomes more vascularised. Therefore, during regeneration or repair of injured tissue muscles, it is unsurprising that it involves concurrent tissue revascularisation to restore blood supply [85, 86]. Thus the inhibition of capillary development due to high degree of $O_2^{\cdot-}$ generation was shown because of SOD^3 deficiency in an experimental setting [87]. These endogenous antioxidant enzymes are known to obstruct the development of fibrosis within the body skeletal muscle. Galasso, Schiekofer, Sato, Shibata, Handy, Ouchi, Leopold, Loscalzo and Walsh [88] reported that the deficiency of GPx-1 protein hinders the rehabilitation of blood flow. It has been reported that the consequence of antioxidant enzymes on skeletal muscle regeneration are imputed to the accumulated viability of myogenic precursors under oxidative stress. Such protective prospective was indicated in vivo for GPx and CAT may inhibit myogenic proliferation [89-91]. However, aside the enzymes found in mammalian cells which represent the basic primary endogenous antioxidant, there are other enzymes that constitute the second phase of antioxidant defence in skeletal muscle cells. These include γ-glutamyl cysteine synthetase (GCS) and heme oxygenase-1 (HO-1). They do not play a sole part in the scavenging of ROS, but also play a role in synthesizing of non-enzymatic antioxidants system that are present in skeletal muscle such as GSH by GCS or biliverdin and bilirubin by HO-1 [44, 91].

Antioxidant enzymes and cellular longevity

The longevity of a life span in relation to age-related diseases is dependent upon certain factors that are responsible in the prolonging or shortening of the body cells [92]. These include free radical reactions, ROS which is the main factor, while others may involve reactive aldehyde errors that arise from biochemical processes [93]. Aging is caused as a result of the accumulation of molecular damages to body cells and tissues [94]. Because of their potential harmful effects of ROS, excessive ROS must be promptly neutralized and eliminated from the cells by

a variety of antioxidant defence mechanisms. Increase in calorie increases the activity of mitochondrial aerobic metabolism thus producing more free radicals while calorie reduction retard aging as well as reduces free radicals production [45].

There is a need to prevent damages resulting to aging. This can either be achieved by synthesizing antioxidants *in vivo* in the body cell or obtaining it via dietary source from the environment. Antioxidants are known to maintain stability and control the increase of free radicals caused via the action of oxidative stress in the biological system [6]. Antioxidants are molecules that contain free electrons that can be donated to stabilize ROS [95, 96]. Antioxidants include both hydrophilic and lipophilic molecules for metabolizing ROS. Therefore, antioxidants prolong cellular longevity by slowing down aging in the life span of an individual. These are derived from external sources (exogenous antioxidant) or generated from within the biological system of the body (endogenous antioxidant). These defence mechanisms against ROS are grouped into three antioxidant pathways which include intracellular, extracellular and membrane antioxidants. Intracellular ROS scavenging enzymes (FRSEs), which is the primary system include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). SOD decreases the excessive level of ROS to a harmless reactive H_2O_2, which is further detoxified into water via the action of CAT with GPx enzyme. GPx is one important enzyme in terms of lipid peroxidation as well as the scavenging of OH^- [47]. Detoxification of ROS is controlled by extracellular or membranous antioxidant and compounds such as Vitamins A, C and E, glutathione, NADPH which serves as the secondary system [97].

Endogenous(enzymatic) antioxidants

These are cellular antioxidants that are present in the biological system and play a vital role in maintaining redox balance, thus causing stability in homeostasis [98]. These endogenous antioxidants enzymes mainly include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR). Scavenging of free radicals involves the ability of cells to maintain constant level of these enzymes, thus preventing aging [6]. Superoxide dismutase enzyme catalyses the partitioning of superoxide (O_2^-) which are biologically toxic and deleterious when produced as by-product of mitochondrial metabolic processes into hydrogen peroxide (H_2O_2) and/or harmless molecular oxygen (O_2). Catalase is an enzyme present in the peroxisomes of eukaryotic cells that causes the degradation of hydrogen peroxide (H_2O_2), a cell damaging agent produced during aerobic metabolism thereby completing the detoxification reaction initiated by SOD. GPx and GR enzymes are those that degrade hydrogen peroxide and also reduce organic peroxides, thus helping in creating route for eliminating toxic oxidants in the biological system [99-101]. But in an individual, that is not well nourished where the biological function of the body is unable to metabolised these toxic substances, then the need for dietary source is of paramount thus avoiding the risk of damage.

Exogenous(non-enzymatic) antioxidants

Exogenous antioxidants are diet derived supplements obtain from plants source and they are of natural origin [102]. These help in scavenging oxidative stress biomarkers in the biological system when enzymatic antioxidant are insufficient to control the net amount of free radical production that exceeds its capacity within the body system, thus maintaining stability [103, 104]. Dietary exogenous antioxidants help to control the level of ROS in order to minimise oxidative damage [105].

These active metabolites that reduces the concentration of ROS which is toxic to the body are gotten from a variety of food and beverages such as coffee, tea, vegetables, fruits, cocoa shells, olives, garlic, ginger, red onion skin, grapes, apple cuticle, nutmeg, mustard leaf seed, peanut seed coat and are used as complementary medicine supplements [106, 107]. Some of these basic metabolites include vitamins C, vitamins E and vitamins A, β-carotene, polyphenols, carotenoids, catechin, Epigallocatechin gallate (EGCG), flavonoids, and selenium [108]. They all contribute to protecting the cells against free radical damage. Vitamin E, also known as tocopherol, is widely distributed in nature and it is the primary antioxidant in cell membranes [109]. Vitamin C (ascorbic acid) is hydrophilic, thus making it effective in aqueous environment. Ascorbic acid directly scavenges free radicals as well as playing a part in vitamin E recycling [110].

Carotenoids are lipid soluble antioxidants having their abilities from their structural arrangement which allows for the scavenging of free radicals [111]. According to Maestri, Nepote, Lamarque and Zygadlo [112], these metabolites have shown in past studies that they contain antioxidant properties which are used as therapy in the control of a number of metabolic diseases. For optimal level of defence and protection from oxidative damage, a biological system will need supplementary exogenous antioxidant which is seen as a potential prophylactic agent that can aid in terms of health and disease management [113]. This has drawn much attention from both the food industry and local consumers with specific attentiveness to the family of the polyphenols because they are present almost everywhere, thus potentially elucidating the high intake of fruits and vegetables [106]

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Antioxidants action in oxidative damage prevention

Enzymatic and non-enzymatic antioxidants subsequently act on free radicals that causes oxidative damage to the body system (figure 3). Enzymatic antioxidants: The main antioxidant enzymes are superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase.

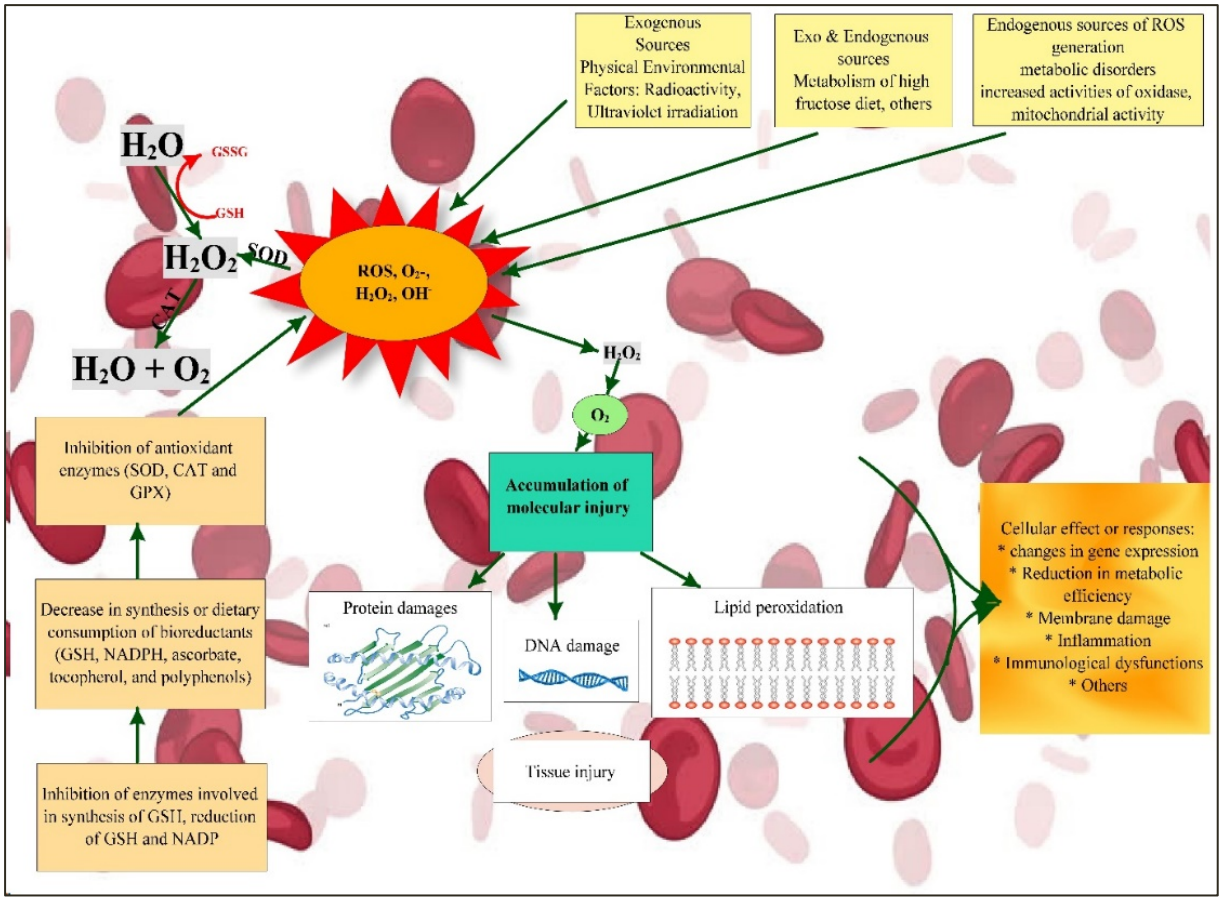

Figure 3 Source of free radical production and damages to biological system

Enzymatic antioxidants

Superoxide dismutase (SOD)

This enzyme which was discovered in 1969 protects against superoxide radicals. The function of SOD is the dismutation of superoxide to form hydrogen peroxide and oxygen. Three isoforms are reported with each having a core metal at its catalytic site which activates the breakdown of superoxide anions [114, 115]. One is present in the extracellular space, while the other two are within the cell. The first isoform which is located in the cytosol and mitochondria has copper-zinc as its cofactor, the second sited in mitochondrial matrix has manganese as its cofactor while the third located in the extracellular space makes use of copper-zinc as its cofactor [116]. Furthermore, superoxide radicals are not known to be extremely reactive, they have been shown to effectively extract electrons from membranes causing electron imbalances in biological membranes through the production of free radicals [117]. This necessitates the need to keep super oxides in check. Mutations in the first isoform of SOD have been reported to cause apoptosis of spinal neurons leading to amyotrophic lateral sclerosis [118]. In skeletal muscle fibers, about 15 to 35% activity of total SOD is effected inside the mitochondria with about 65-85% remaining within cytosol [78]. In the oxidative fibers; these activities to a higher degree are significant (e.g. type I fibers) when compared to those muscles whose volumes of mitochondria are low (e.g., type IIx fibers).

Glutathione peroxidase (GPx)

It was reported that about five different mammalian GPx exist in the biological system [119, 120]. They function basically in the catalysis of hydrogen peroxide to water, or alcohol depending on whether the hydrogen peroxide is organic or not using reduced glutathione (GSH) [121]. The reduced GSH are oxidized to glutathione disulphide (GSSG) after donating electrons. Each form of GPx is substrate specific though they carry out similar reactions. The reality is that GPx can decrease various hydroperoxides, making them crucial intracellular antioxidants in

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preserving the system against the action of ROS-mediated cell deterioration [122]. The reduction of GSSG back to GSH after it has been reduced is carried out by the enzyme glutathione reductase using NADPH as the energy source [122].

Catalase (CAT)

It breaks down hydrogen peroxide by catalyzing it to water molecule and oxygen. CAT is widely distributed having iron as its cofactor attached to its active site [115]. CAT has a lower affinity for hydrogen peroxide compared to GPx (i.e., GPx Km = 1μM vs. CAT Km = 1mM), but it has the highest activity in an extremely oxidative muscle fibers and small in fibers with decreased oxidative capacity compared to both SOD and GPx [122, 123]. Along the primary antioxidant enzymes, other additional enzymes that participate in redox balance are also present. These include the thioredoxin (TRX), peroxiredoxin (PRX) and glutaredoxin (GRx). More on these can be seen in different studies [124-126]

Non-enzymatic antioxidants

Reportedly, the most important muscle fiber non-enzymatic antioxidant is GSH, and it is the most abundant non-protein thiol in cells [127]. GSH which is produced in the liver varies in concentration across different organs based on their functions [128]. That is why tissues with oxidants contain more amounts of GSH. The GSH in skeletal muscles is based on the fiber types as shown in type I fibers in rats which contain 4-5 fold greater amount of GSH compared to type IIb [129]. Many studies showed that skeletal fibers have the ability to remodel themselves in climax intensity of tolerance during exercise when they increase glutathione (GSH) magnitude in the cell [129, 130]. This process is due to increased activity of ɣ-glutamylcysteine synthetase known as the rate limiting enzyme; which is GSH biosynthesis [131].

Another important non-enzymatic antioxidant is α-lipoic acid, a natural compound present in a variety of foods [132]. It serves as cofactor for α-dehydrogenase complexes and participates in some cellular reactions as well. It has been concluded by many studies that α-lipoic acid can recycle vitamin C [133]. Light exercise may increase its level in skeletal muscle fibers, but prolonged and constant exercise does not [133]. Other known non-enzymatic antioxidants are uric acid, bilirubin, biliverdin, and coenzyme Q10 [134].

Conclusion

There is no doubt that high ingestion of fructose can cause devastating effect to the body and consequently, result to metabolic complication that are deleterious to the body muscular tissue; with the influx of industrialised dietary foods of high sugar content supplementation of exogenous antioxidant had showed the tendency to attenuate fructose-induced oxidative damage by suppressing the levels of free radicals which also resulted to the activation of endogenous antioxidant enzymes that are part of the antioxidant defence mechanism in the body. These reviews provide evidence supporting the benefit of exogenous antioxidant supplement that can help in regulating and scavenging excess free radical's production to ameliorate oxidative stress/damage in our growing world thus decreases the risk of complications as well as mortality.

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