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# A Review on Free Radicals and Antioxidants

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**Abstract**

Free radicals are small diffusible molecules that are highly reactive because of the unpaired electron. Free radicals were initially thought to be oxygen centred radicals called reactive oxygen species (ROS) but also include a subgroup of reactive nitrogen species (RNS) and are all a product of normal cellular metabolism. Oxygen is necessary for energy production via the electron transport chain in living organisms, a mechanism by which energy (ATP) is released to enable the cell carry out its normal physiological functions. This is attributed to its high redox potential which makes it a brilliant oxidizing agent capable of easily accepting electrons from reduced substrates. This contradictory effect of oxygen in living organisms necessitated the evolution of antioxidant system to protect against over oxidation and combat reactive oxygen species (ROS). The mitochondria are the most vital source of ROS production. Just like free radicals, antioxidants can be endogenously produced and reduced glutathione and can also be introduced to the biological system exogenously, usually through diet. Antioxidants primarily function to balance out free radicals generated during metabolic processes including during mechanisms involved in protecting the gut from inflammation and injury.

**Keywords:** Free radicals, antioxidants, inulin, tocopherol

## Introduction

### Free Radicals

The first uproar of interest into research about free radicals and their effect on the biological system was triggered by studies by Denham Harman in 1956 of the role of free radicals in the aging process (Droge, 2002). The second major exploration of free radicals in biological system was in 1969 by McCord and Fridovich which led to the discovery of superoxide dismutase (SOD) hence, providing substantial evidence of the relevance of free radicals in biological systems (Droge, 2002). The third era of free radicals exploration started from 1977 when Mittal and Murad produced evidence that hydroxyl radical ($OH^{\bullet}$), stimulates activation of guanylate cyclase and formation of the "second messenger" cyclic guanosine monophosphate (cGMP) (Droge, 2002). Afterwards, a lot of evidence has been provided to show that biological system have

adapted to a coexistence between free radicals and have developed numerous productive use of free radicals in numerous physiological functions (Lobo *et al.*, 2010; Lushchak, 2014;Eze et al.,2016).

Oxygen is necessary for energy production via the electron transport chain in living organisms, a mechanism by which energy (ATP) is released to enable the cell carry out its normal physiological functions (Barja, 2004). This is attributed to its high redox potential which makes it a brilliant oxidizing agent capable of easily accepting electrons from reduced substrates. This contradictory effect of oxygen in living organisms necessitated the evolution of antioxidant system to protect against over oxidation and combat reactive oxygen species (ROS) (Rahman, 2007 ; Ziech *et al.*, 2010).

Free radicals are small diffusible molecules that are highly reactive because of the unpaired electron (Ziech *et al.*, 2010). Free radicals were initially thought to be oxygen centred radicals called reactive oxygen species (ROS) but also include a subgroup of reactive nitrogen species (RNS) and are all a product of normal cellular metabolism (Droge, 2002). ROS and RNS have been established to play a double role as beneficial and harmful specie based on their beneficial and deleterious effect on biological systems (Valko *et al*., 2006). The beneficial roles occur at low to moderate concentrations while the deleterious effects occur at high concentrations where the ROS/RNS production surpasses the antioxidant ability to balance it. As secondary messengers, these free radicals interrupt normal physiological processes at different stages which initiate a series of harmful chain reactions that lead to molecular damage of biological tissues and signalling mechanism (Victor *et al*., 2004).

The deleterious effect caused by ROS/RNS that results in biological damage is termed oxidative stress and nitrosative stress (Aruoma, 1998). Excess ROS can cause harm to cellular lipids, proteins or DNA thereby disrupting their normal function (Droge, 2002). The adequate balance of beneficial and deleterious effect of free radicals in the living organism is attained through a mechanism called "redox regulation" thus maintaining a redox homeostasis (Barja, 2004)). Members of the reactive oxygen species include singlet oxygen, superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), peroxyl radical (ROO) and the very reactive hydroxyl radical (OH) (Droge, 2002 ; Van den *et al*., 2011). Free radicals derived from the reactive nitrogen specie include nitric oxide (NO) and peroxynitrite anion (ONOO) (Victor *et al.*, 2004). Exogenous sources of free radicals are radiation, drugs, xenobiotics, toxins etc (Van den *et al.*, 2011). Endogenous sources of free radicals involve mechanisms that are usually more complex and extensive and some examples are briefly discussed below.

## Mitochondria

The mitochondria are the most vital source of ROS production (Victor *et al.*, 2004). During the physiological process of ATP generation via the respiratory chain, molecular oxygen is reduced to two water molecule (Droge, 2002). However, during energy transduction some electrons 'leak' prematurely thereby necessitating the incomplete conversion of about 1-2% of molecular oxygen into superoxide anion radical. Superoxide radical chemical reactivity is relatively weak due to its inability to pass through lipid membrane and its quick conversion to hydrogen peroxide by the antioxidant super oxide dismutase (SOD). Nevertheless, $H_2O_2$ produced may lead to the generation of a more chemical reactive molecule; the hydroxyl radical through the reaction of $H_2O_2$ with iron in the Fenton reaction (Victor *et al*., 2004).

## Cellular Oxidase

Although mitochondrial respiratory chain is the main source of superoxide, this free radical specie can also be produced by one- electron reduction of oxygen by numerous different oxidases under certain conditions (Ray and Shah, 2005). These oxidases include NAD(P)H oxidase (NOX family) and Xanthine oxidase (XO) (Droge, 2002). NOX enzymes can be found in the lymphocytes, fibroblasts, endothelial cells, myocytes and chondrocytes where moderate amount of ROS are produced and act as a

regulator of cellular response on exposure to infections and microbial invasion (Ray and Shah, 2005). An activation of NOX family enzymes is followed by "respiratory burst" which leads to increased oxygen consumption, glucose utilization and increased production of reduced nicotinamide phosphate dinucleotide (NADPH) by the pentose phosphate pathway (Ray and Shah, 2005).

Another distinguished source of superoxide anion is Xanthine oxidase (XO), a non-heme enzyme that is usually found in the cytosol especially during hypoxic conditions (Droge, 2002). Under physiological condition, XO which is a Xanthine oxidoreductase (XOR) exists in the dehydrogenase form but during hypoxia it is converted to an oxidase form that have the capability of producing superoxide (.O-2) and hydrogen peroxide ($H_2O_2$) by using oxygen as an electron acceptor (Ray and Shah, 2005).

## Metal catalysed reactions

The Hydrogen peroxide produced during hypoxia by the XO is likely to face different cellular fates, such as, detoxification to $H_2O$ and $O_2$ by the glutathione peroxidise (GPx) (in the mitochondria, together with gluthathione reductase) and catalase in peroxisomes or it can act as a precursor for more reactive species such as hydroxyl radical (HO•) (Droge, 2002)). HO• produced from this reaction is the strongest oxidizing agent known and reacts with organic molecules through diffusion limited rates.

Haber and Weiss demonstrated that superoxide and $H_2O_2$ leads to the production of the highly deleterious hydroxyl radical (HO•) and initiates the oxidation of organic substrates by Haber-Weiss reaction (Droge, 2002)

$O^{2-} + H_2O_2 = HO\bullet + OH^- + O_2$

(Haber - Weiss Reaction).

However, this reaction to produce HO requires a metallic constant ($CU^{2+}$ or $CU^{3+}$) to proceed and is a combination of transition metal mediated chemical reactions called Fenton reaction (Victor *et al.*, 2003)

$Fe^{3+} + .O2- = Fe^{2+} + O_2$
$Fe^{2+} + H_2O_2 = Fe^{3+} + OH^- + HO\bullet$
(Fenton reaction)

## Myeloperoxidse

Myeloperoxidase is found mainly in neutrophils with lower levels in monocytes and eosinophils. As seen in the reaction below, hydrogen peroxide ($H_2O_2$) can also be converted to another free radical HOCL by reacting with chloride (CL-) ions through enzyme myeloperoxidase (MPO) – catalyzed reaction (Droge, 2002).

$H_2O_2 + Cl^- = HCIO + HO\bullet$

Radicals produced from oxygen represents the most important class of free radicals generated in living organism (Valko *et al.*, 2007). During respiratory process, $O_2$ is progressively reduced by a controlled supply of four electrons to yield $H_2O$. During this reduction process in normal biological system, the electrons are transferred either from the electron transfer chain (4- electron reduction) or at random from the organic/inorganic species in their immediate environment (1- electron reduction). Nevertheless, the incomplete reduction of $O_2$ is possible and often leads to formation of chemical entities that are still potent oxidants. Depending on if it is a one-, two- or three- electron reduction, $O_2$ may generate successively superoxide radical anion ($O^{\bullet-}_2$), hydrogen peroxide ($H_2O_2$) or hydroxyl radical ($OH^{\bullet}$). Modern use of the term reactive oxygen species includes both oxygen radicals and non-radicals that are easily converted into free radicals ($0_3$, $H_2O_2$, $^1O_2$) (Halliwell, 1994)

## Singlet Oxygen ($^1O_2$)

$^1O_2$ is produced from the molecular oxygen by means of electron transfer, with inflammatory processes and photosensitization being the major sources (Droge, 2002). Through a series of reactions involving myeloperoxidase (MPO), $O_2$ is formed. Other ways by which $^1O_2$ is produced are dismutase of superoxide formed in NADPH

oxidase reaction, disproportionation of the $H_2O_2$ with peroxynitrite or hypohalites and reaction of hydroperoxides with peroxynitrite (Ray and Shah, 2005)

$2O_2 + NADPH = 2O_2^- + NADP+ + H^+$
$2O_2^- + 2H = H_2O_2 + {}^1O_2$
$2O_2^- + 2H^+ = H_2O_2 + O_2$
$H_2O_2 + Cl^- = H_2O + OCl$
$H_2O_2 + OCl\text{-} = 1O_2 + H_2O + Cl^-$

The singlet oxygen radicals cause deleterious effect to DNA particularly through oxidation of guanine residues leading to G:C to T:A transverse during replication and then to mutations.

## Superoxide

Molecular oxygen (dioxygen) forms the superoxide anion radical ($O\cdot^-_2$) when it receives an electron. $O\cdot^-_2$ are produced mainly in the mitochondrial electron transport chain during ATP generation (Droge, 2002, Valko *et al*, 2007). These superoxide radicals are considered primary ROS and can produce secondary ROS through interaction with other molecules directly or indirectly through enzymatic or enzyme catalyzed reactions. Depending on the environment and PH. Superoxide radical can exist as hydroperoxyl at low PH. Under normal physiological PH $O\cdot^-_2$ exist in the charged form unlike hydroperoxyl (Droge, 2002). However, hydroperoxyl is physiologically important because of its ability to penetrate biological membranes easily than the charged $O\cdot^-_2$. $O\cdot^-_2$ acts a powerful nucleophile and is also capable of accepting H+ from compounds capable of donating it (ascorbate and tocopherol). More significantly, superoxide radicals has the ability to undergo dismutation where one superoxide radical react with another superoxide radical leading to formation of oxygen and hydrogen peroxide (Valko *et al.*, 2007))

## Hydrogen Peroxide ($H_2O_2$)

This is a product of dismutation reaction of superoxide radicals (Droge, 2002). Under physiological conditions, peroxisomes are the major producers and consumers of $H_2O_2$ . They are not really free radicals but contain free electrons. They are therefore considered reactive oxygen species because of ability to react with biomolecules and be harmful to cells (Victor *et al.,* 2003). Furthermore their high solubility in aqueous solution makes them easily penetrate biological membranes conferring on them highly deleterious properties. The enzyme catalase is also found in peroxisome and helps to decompose $H_2O_2$ hence maintaining a homeostatic balance (Barja, 2004). A disruption of this balance can lead to direct degradation of heme proteins by $H_2O_2$, release of iron, inactivation of enzymes and oxidation of DNA, lipids, -SH groups of proteins and keto acids ( Halliwell, 2000). $H_2O_2$ also serve as a source for more toxic species such as OH and HCIO (Droge, 2002).

## Hydroxyl Radical ($OH^{\bullet}$)

The hydroxyl radical is a neutral form of hydroxide ion possessing very high reactivity that makes it a very deleterious radical (Droge, 2002). Hydroxyl radicals are short lived species with a half life of $10\text{-}^9$ unlike superoxide radicals that are relatively stable; hence react with molecules at close proximity with high affinity (Droge, 2002). $OH^{\bullet}$ is produced by two major biochemical reaction called Haber-Weiss reaction and Fenton reaction (as earlier discussed). Under conditions of stress, superoxide radicals release “free iron” from iron containing molecules required to react with $H_2O_2$ in the Fenton reaction to form hydroxyl radicals (Lobo *et al*., 2010).

## Reactive Nitrogen species (RNS)

Reactive nitrogen species (RNS) are nitrogen-containing free radicals which possess high oxidizing ability hence involved in promoting oxidative stress (Aruoma, 1998). They are most times classified as part of reactive oxygen species (ROS) but the term reactive oxygen and nitrogen species (RONS) has also been used in literatures (Droge, 2002). The main RNS include nitric oxide (NO.) and nitrogen dioxide ($.NO^{-2}$) together with non-radicals such as peroxynitrite (ONOO-) besides others (Blaise *et al.,* 2005). Below is a brief insight into nitric oxide and peroxynitrite.

## Nitric Oxide

Nitric oxide (NO) is a small molecule that contains one unpaired electron on the antibonding hence a radical. In 1992 NO was acclaimed "molecule of the year" in science magazine because of its extraordinary properties (Habib and Ali, 2011). It is soluble in aqueous and lipid media, a property that enables it to readily diffuse through cytoplasm and plasma membranes (Habib and Ali, 2011). It has a half-life of only a few seconds in aqueous environment and a greater stability in environment with lower oxygen concentration (half-life of more than 15seconds). In extracellular milieu NO reacts with oxygen and water to form nitrate and nitrite anions. $NO^{\cdot}$ is generated in biological tissues through a tightly regulated process by specific nitric oxide synthases (NOSs) which exists in three isoforms, Neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) (Blaise et al., 2005). These nitric oxide synthases metabolise L-Arginine to L-Citruilline with the formation of $NO^{\cdot}$ via a five electron oxidative reaction.However many tissues express one or more of these isoforms. While nNOS and eNOS are constitutively expressed and their activity is regulated by the intracellular calcium concentration, the isoform iNOS is inducibly expressed in macrophages folllowing stimulation by lipopolysaccharides, cytokines and other agents (Habib and Ali, 2011). Expression of iNOS is regulated at the transcriptional and post transcriptional level by signalling pathways involving redox-dependent transcription factor NF-KB or mitogen activated protein kinases (MAPKs) (Ray and Shah, 2005).

NO is known to act as secondary messengers controlling various physiological functions such as neurotransmission, blood pressure regulation, defence mechanism, smooth muscle relaxation and immune regulation. The regulation of vascular tone by cGMP is unique. The enzyme soluble guanylate cyclase (sGC) is known to be activated by both hydrogen peroxide and NO (Victor *et al.*, 2004 ; Droge *et al*, 2002). Guanylate cyclase belongs to the family of heterodimeric heme proteins and catalyses the formation of cGMP, which is used as an intracellular amplifier and secondary messenger in a variety of physiological responses. NO binds to $Fe^{2+}$ - Haem group in sGC resulting in a conformational change at $Fe^{2+}$ that activates the enzyme. Its product cGMP modulates the function of protein kinases, ion channels and other physiologically important targets, the most relevant ones being regulation of smooth muscle tone and inhibition of platelet adhesion.

During inflammatory process, cells of the immune system produce both nitric oxide and superoxide through oxidative burst (Victor *et al.,* 2004). Under these conditions, nitric oxide and superoxide anion may react together to produce significant amounts of a much more oxidatively active molecule, peroxynitrite anion ($ONOO^{-}$) which is a potent oxidizing agent that can cause DNA fragmentation and lipid oxidation (Velayutham *et al.*, 2011).

$NO + O_2 = ONOO$

NO toxicity is predominantly linked to its ability to combine to superoxide anions (May and Qu, 2011). NO also readily binds certain transition metal ions: in factmany physiological effect of NO are expressed as a result of its initial binding to $2Fe^{2+}$ - Haem group in the enzyme soluble guanylate cyclase (sGC) . $Fe^{2+}$ (sGC) + $NO^{\cdot}$ = $Fe^{2+}$ (sGC) – NO (represented as ($F^{2+}$ - NO)), however, ($Fe^{3+}$ - NO) is also commonly seen (May and Qu, 2011).

## Antioxidants

Just like free radicals, antioxidants can be endogenously produced (e.g superoxide dismutase (SOD) and reduced glutathione (GSH))) and can also be introduced to the biological system exogenously, usually through diet (e,g vitamin c, caratenoids and vitamin E (Halliwel, 2011) (Amber *et al.,* 2013). Antioxidants primarily function to balance out free radicals generated during metabolic processes including during mechanisms involved in protecting the gut from inflammation and injury (Rahman, 2007 ; Poljsa *et al*., 2011). Antioxidants can be said to go about its defence system in three main ways; by proteins sequestering with transition metals preventing

their availability for reaction with free radicals thus inhibiting their deleterious effect, making available small molecules that have the capability of scavenging free radicals and through specific mechanisms for the correction of ROS-induced DNA damage (Foyer, 2005). Endogenous antioxidants can further be classified into enzymatic or non-enzymatic. Enzymatic antioxidants are superoxide dismutase (SOD), catalase and the glutathione system (Rahman, 2007;Ofor et al.,2016;Nwosu et al.,2016; Nwosu et al.,2015; Nwosu et al.,2016)

## Superoxide dismutase

SODs are a class of closely related enzymes that catalyse the breakdown of the superoxide anion into oxygen and $H_2O_2$ present in almost all aerobic cells and in extracellular fluids (Rahman, 2007). It comprises of 3 families depending on the metal co-factor; Cu/Zn, Fe and Mn and the Ni type which binds nickel. Mn-SOD has been found mostly in mitochondria and peroxisomes, Fe-SOD has been found in peroxisomes and CuZn-SOD in peroxisomes and cytosol (Droge, 2002 ; Valko et al., 2007) . Furthermore, three forms of SOD are said to be present; SOD1 (in the cytoplasm), SOD2 (in the mitochondria) and SOD3 (extracellular), with SOD1 and SOD3 containing copper and zinc as their reactive centre and SOD2 containing manganese as its reactive centre (Victor *et al.,* 2004).

Superoxide dismutase's converts superoxide to hydrogen peroxide ($H_20_2$) (Halliwell, 1994)

$$2O_2^{\cdot-} + 2H^+ \longrightarrow H_2O_2 + O_2$$

## Catalase

This is predominant in cells exposed to oxygen and is frequently used to catalyse the decomposition of $H_2O_2$ (by product of a range of normal metabolic processes) to oxygen and water (Schwentker et al., 2002). Catalase has one of the highest turnover rates for all enzymes; with one molecule of catalase being able to convert approximately 6million molecules of $H_2O_2$ to water and oxygen each minute. It can be found in all organs but predominantly in the liver (Droge, 2002 ; Valko *et al.,* 2007).

## Glutathione system

The Glutathione system comprises of four main classes; Glutathione reductase, Glutathione peroxidise (GPx)(competes with catalase for $H_2O_2$ and is the major source of protection against low levels of oxidative stress) and Glutathione S-transferase (Rahman, 2007).

Non enzymatic antioxidants includes but are not limited to; Glutathione (GSH), ascorbic acid(Vitamin C), tocopherols and tocotrienols (Vitamin E) , uric acid, melatonin, alpha lipoic acid (Valko *et al.,* 2007).

## Glutathione

They are synthesized from constituent amino acids in cells. It is a cysteine containing peptide. The thiol group in its cysteine moiety is a reducing agent that can be reversibly oxidized and reduced. In cells it is maintained as Glutathione reductase which subsequently reduces other metabolites and enzyme systems while still capable of reacting with oxidants. It plays a pivotal role in maintaining cells redox state hence recognized as one of the most important cellular antioxidant (Rahman, 2007).

## Melatonin

This is a powerful antioxidant that has the ability to easily cross cell membranes and blood-brain barrier. Unlike other antioxidants melatonin does not undergo redox recycling (repeated reduction and oxidation),once oxidized cannot be reduced to previous state because it forms several stable end products when it reacts with free radicals. Thus has been termed terminal (or suicidal) antioxidant (Gutteridge, 2004 ; Rahman, 2007)

## Ascorbic acid (Vitamin C)

Vitamin C is usually maintained in the reduced form in the body by its reaction with glutathione which can be catalysed by protein. Vitamin C is able to prevent formation of nitrosamines,

neutralise ROS such as $H_2O_2$, thus boosting immunological response (Victor *et al.*, 2007).

## Uric acid

Accounts for roughly half the antioxidant ability in plasma. Uric acid is thought to have substituted ascorbate in evolution (Rahman, 2007). Just like ascorbate, uric acid is capable of initiating production of free radical species.

## Vitamin E

**T**hey are fat soluble vitamins that exist in eight different forms and possess antioxidative properties. The main function of vitamin E is protecting the cell from lipid peroxidation. In the human biological system, α-tocopherol is the most studied and is said to have the highest bioavailability with the body preferentially absorbing and metabolizing this most active form. α- Tocopherol is claimed to be the major membrane bound antioxidant employed by the cell.α-tocopherol reacts with lipid radicals in the lipid peroxidation reaction to form α –tocopherol radical which can be reduced back to its original form by ascorbic acid, retinol or ubiquinol. Their ability to protect cell membranes inturn helps to prevent premature keratinisation.

It has been postulated that even though ROS is deleterious to cell macromolecules such as proteins, DNA and proteins, lipid peroxidation is of utmost importance because of it easy propagation of free radical reaction with effects such as changes in the fluidity of cell membrane, increased membrane permeability, reduction in ability to maintain an equilibrated concentration gradient of concentration and inflammation (Cejas et al., 2004). Hence, the highly deleterious effect of lipid peroxidation has led to the magnification of the importance of PH-GPx ; an antioxidant which protects against lipid peroxidation by primarily reducing lipid peroxides in cell membranes. PH-GPx metabolises phospholipid hydro peroxides in cell membranes utilizing GSH or other reducing equivalents.

Animal and laboratory studies have shown that higher levels of exogenous antioxidants have helped avoid free radical cell damages linked to cancer development (a standard intake dose is yet to be established in relation to the different cancer types and for diseases caused by free radicals) but observational studies carried out to investigate whether developing cancer can be prevented by exogenous antioxidant intake have produced mixed results. Randomised controlled clinical trials believed to provide the most powerful and highly dependable proof of the advantages and/or harm of a health related intervention to date, have only nine trials for the association of dietary antioxidant supplement in cancer prevention conducted worldwide and have shown no positive effect in cancer prevention with none exploring the association of tocopherol to colon cancer prevention.

## Inulin as an exogenous antioxidants

## The Effect of Probiotics and Inulin (prebiotic) on the Gastro Intestinal tract Microbiota

The gastro intestinal tract consists of a wide range of microorganism referred to as gut microbiota which shares a commensal relationship with the host. This gut microbiota predominantly consists of four main groups of bacteria belonging to the genus *Bacteroidetes* (23%), *Firmicutes* (64%), *Proteobacteria* (8%) and *Actinobacteria* (3%) (Meyer and Stasse, 2009).

.The gut microbiota plays various roles which includes but not limited to, renewal of epithelial cells of the intestine, food metabolism, regulation of the immune system and influence on peristalsis. These microorganisms are not easily leached out of the body because they have the ability to adhere to the intestinal wall and grow rapidly (Apajalahti, 2005).While bacteria's that produce enzymes that facilitates absorption and distribution of nutrients are most relevant, species such as *Lactobacillus acidophilus* and *Streptococcus salivarius* which have the capability of defending against bacteriophages and weaken acute immune response are equally important. The gut microbiota is able to perform their immunomodulatory role through their effect on cytokine levels and interaction with gut-associated lymphoid tissue; the biggest lymphatic

organ in the body which produces 70% to 80% of the immune cells (Kolida *et al.,* 2002). The gut microbiota also carries out their protective functions by competing with pathogenic bacteria for available nutrients in the environment and the receptors present on the epithelial wall (Apajalahti, 2005).

Moreso, the gut microbiota produce antimicrobial agents such as bacteriocins and they are also capable of inhibiting the growth of bacteria synthesizing carcinogens such as *Bacteroides spp, Streptococcus bovis* and *Citrobacter rodentium* with some of the microbiota having the ability to metabolize dietary carcinogens (Wasilewski *et al.,* 2015). Microbiotas play important structural role through strengthening the tightness of the intestinal barrier (Van den Den *et al.,* 2011). This is made possible by influencing the expression of some structural proteins constituting tight junctions between enterocytes and facilitating the synthesis of immunoglobulin A. Furthermore, microbiotas are able to carry out metabolic functions that affect cell proliferation and differentiation of epithelial of the intestine by providing energy source such as butyrate and short chain fatty acids (SCFAs) to the epithelium (Wasilewski *et al.,* 2015). Intestinal microbiota also plays a role in the transformation of steroids and fatty acids as well as in the fermentation of dietary fibre and ions. Additionally, intestinal microbiotas synthesize various B-group vitamins and vitamin K.

According to the definition by World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations, probiotics are living organisms which when administered in adequate amounts, confers health benefit to the host. The "grandfather" of modern probiotics, Ilya Mechnikov, a Nobel laureate in Medicine made the first observation of the therapeutic effect of bacteria in 1908 when he drew attention to the relationship between a very good general state of health and longevity of the Bulgarian rural population and systemically ingested sour milk containing lactic acid bacteria (*Lactobacillales)*, which he called "the Bulgarian bacillus". Although the mechanism of action of most probiotic is yet to be fully understood, they have been reported to be commonly used for the treatment of inflammatory diseases such as arthritis, ulcerative colitis, Crohn's disease, antibiotic-induced diarrhoea. A study reported the levels of IL-1β, TNF-α and C-reactive protein to be significantly reduced in the serum of the group receiving probiotic yogurt with an increase in IL-6 and IL-10 as opposed to the placebo group, proposing that probiotics may contribute to the homeostasis of the GIT and modulate pro and anti-inflammatory response of the immune cells of the intestines (Wasilewski *et al.,* 2015). Presently, most of the published trials on probiotics were carried out using a preparation called VSL#3 which contains eight strains, namely,*Lactobacillus casei, Lactobacillus bulgaricus, Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium brevis* and *Streptococcus thermophiles* (Wasilewski *et al.,* 2015). It has been observed that the administration of VSL#3 greatly increases the levels of IL-10 and IL-1β while inhibiting the production of IL-12. It was also found that the use of VSL#3 increases the expression of proteins responsible for the formation of tight junctions and reducing the number of apoptotic epithelial cells thus strengthening the integrity of the intestinal epithelial barrier.

Inulin as a prebiotic is a food ingredients whose distinctive property is their resistance to digestive enzymes produced by the human body but remain susceptible to fermentation by colonic bacteria's (Wasilewski *et al.,* 2015). The fermentation they undergo in the colon by anaerobic bacteria metabolizes this oligosaccharide to SCFAs, such as butyrate, propionate and acetate which selectively stimulate the growth of bifidobacteria. This induces bifidogenic effects with a decrease in intraluminal PH (Meyer and Stasse-Wolthuis, 2009). While the bifidogenic effect stimulate the growth of this beneficial bacteria, the decrease in intraluminal PH plays a significant role in the prevention of diarrhoea and inhibition of the growth of some strains of potentially pathogenic bacteria such as Clostridium spp. SCFAs increases the synthesis of intestinal mucus, improves mucosal barrier function, stimulate

production of regulatory T cells (Treg) and immunosuppressive cytokines (e.g IL-10) and reduce the amount of proinflammatory mediators. It has been reported that the administration of prebiotic improves the structure and function of the intestinal barrier by decreasing the activities of the endocannabinoid system (ECS) in the gut while increasing the level of GLP-2; which stimulates the production of proteins that form the tight junctions. A combination of probiotics and prebiotics is called synbiotics and is believed to employ synergistic effect yielding a more potent result (Pasqualetti *et al.,* 2014).

## Conclusion

Free radicals are small diffusible molecules that are highly reactive because of the unpaired electron. Oxygen is necessary for energy production via the electron transport chain in living organisms, a mechanism by which energy (ATP) is released to enable the cell carry out its normal physiological functions. This is attributed to its high redox potential which makes it a brilliant oxidizing agent capable of easily accepting electrons from reduced substrates. This contradictory effect of oxygen in living organisms necessitated the evolution of antioxidant system to protect against over oxidation and combat reactive oxygen species (ROS). The mitochondria are the most vital source of ROS production. Just like free radicals, antioxidants can be endogenously produced and reduced glutathione and can also be introduced to the biological system exogenously, usually through diet. Antioxidants primarily function to balance out free radicals generated during metabolic processes including during mechanisms involved in protecting the gut from inflammation and injury.

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