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A Review on Oxidative Stress and Arthritis

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Abstract:
Arthritis is a disease from which people are suffering throughout the world. We are mainly focusing our discussion of Rheumatoid Arthritis and Osteoarthritis. Both Rheumatoid Arthritis and Osteoarthritis are resulting from the generation of free radicals due to oxidative stress. Antioxidants are inhibitors of the generation of free radicals. Antioxidant constituents of the plants (phytochemicals), spices acts as a radical scavenger and convert the highly reactive radicals to less reactive radicals. The causes of the diseases are also explained in the review. The immune system also induced inflammation but it also helps to prevent inflammation. This review presents some information about the oxidative stress and Arthritis, how Arthritis can be treated.

Keywords: *free radicals, oxidative stress, arthritis, Antioxidants*

1. Introduction

Oxygen is the most important element which is indispensible for life. Molecular oxygen is essential for the survival of all aerobic oxygen. Mitochondria produce free radicals by utilizing oxygen (1). Oxidative process that takes place regularly in a cell plays an important role for life and death of a cell. Free radicals are chemical species containing one or more unpaired electron in its balance shell so it is unstable, short life and highly reactive, that is, it reacts with other compounds fast in order to capture the electrons that required to gain its stability. A dot is always used to denote free radicals. Unpairing of molecular oxygen leads to the formation of unstable free radicals. These radicals are highly reactive and lead to the formation of reactive oxygen species that is free radicals. But, most biological molecules are non radical. When a free radical reacts with a non radical, a new free radical is generated (2). For example

$$\geq CH + OH\bullet \rightarrow \geq C\bullet + H_2O$$

$$\geq C\bullet + O_2 \rightarrow \geq C - O - O\bullet$$

peroxyl radical

$$\geq C - O - O\bullet + \geq CH \rightarrow \geq C - O - OH + \geq C\bullet$$

lipid hydroperoxide

Most common free radicals are O^{2-} , H_2O_2, OH., ROOH, RO.,ROO., HOCl are called oxidants. Reactive oxygen species(ROS) is a collective term used for a group of oxidants which are either free radicals or molecular species capable of generating free radicals(3) Free radicals are responsible for tissue damage.

Table 2 Evidence that damage by reactive oxygen (ROS) and nitrogen species (RNS) occurs *in vivo*

Target of damage	Evidence
DNA	Low levels of oxidative base damage products are present in DNA isolated from all aerobic cells; levels often increase in patients with chronic inflammatory diseases or subjected to oxidative stress, e.g. from smoking. Some base damage products are excreted in urine, presumably resulting from DNA repair processes. Smokers and rheumatoid arthritis patients excrete more 8-hydroxydeoxyguanosine (8-OHdG). Elevated 8-OHdG concentrations are frequently observed in animals treated with carcinogens or other toxins.
Protein	Attack of ROS upon proteins produces carbonyls and other amino acid modifications (e.g. methionine sulfoxide, valine hydroxides, 2-oxohistidine, protein peroxides, hydroxylation of tyrosine to DOPA, formylkynurenine). Low levels of carbonyls and certain other products (e.g. *ortho*-tyrosine, valine oxidation products) have been detected in healthy animal tissues and body fluids. Nitrotyrosines, products of attack on tyrosine by RNS, have been detected in atherosclerotic lesions, human plasma and urine; concentrations are higher in body fluids/tissues from patients with chronic inflammatory diseases. Bityrosine has been detected in urine and atherosclerotic lesions.
Lipid	Accumulation of 'age pigments' in tissues. Lipid peroxidation in atherosclerotic lesions. Presence of specific end products of peroxidation (e.g. isoprostanes) in body fluids (including urine); levels increase in plasma during oxidative stress, e.g. in smokers, in CCl_4 treatment of animals, and in premature babies.
Uric acid	Attacked by several ROS to generate allantoin, cyanuric acid, parabanic acid, oxonic acid and other products, which are present in human body fluids. Levels of these products increase in chronic inflammatory/metal overload diseases.

Table 1

In the biological system free radicals are generated from two important sources i) Mitochondrial electron chain (ER oxidation,NADPH oxidase etc ii) Environmental source (drug,pesticides,transition metals). Production of partly reduced oxygen Metabolites are the byproducts of Mitochondrial electron Chain (4). In normal physiology of human being the endogenous free radicals are produced in the body and are neutralized by endogenous antioxidants. An imbalance between the production of reactive oxygen species(ROS) and the biological systems' ability to detoxify readily the reactive intermediate or easily repair the resulting damage is called **oxidative stress**. Imbalance in redox status may develop cellular oxidative stress (5, 6).Depletion of dietary antioxidants and other essential dietary constituents can also lead to oxidative stress. Depletion of ATP and necrotic cell death occurs due to loss of mitochondrial function during elevated oxidative stress whereas moderate oxidation can trigger apoptosis. From the recent study it is evident that induction of apoptosis or necrosis during oxidative stress actually determined by redox state of a cell.

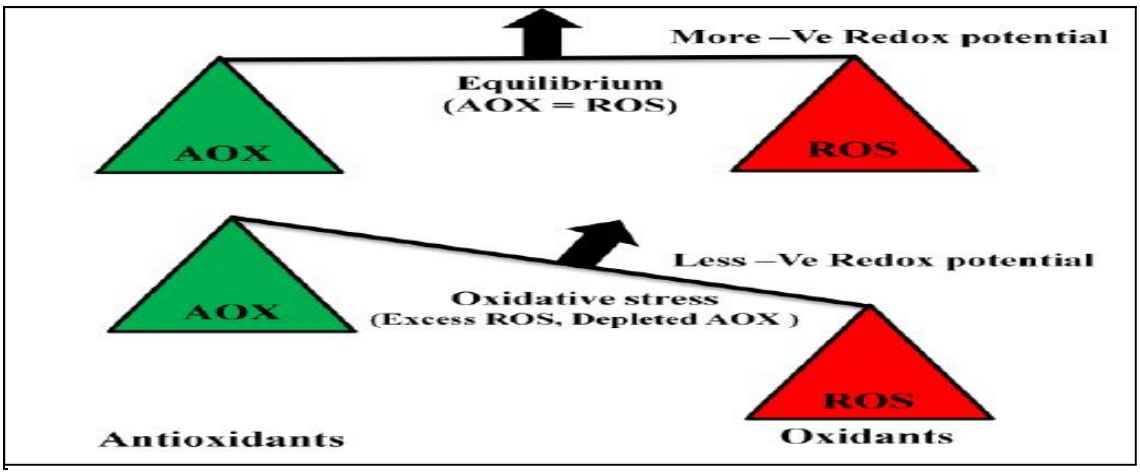

Figure 1

Fig:The balance between oxidant and antioxidants defines oxidative stress
ROS- Reactive Oxygen Species, AOX-Antioxidant
The oxidants that are responsible for oxidative stress are O_2^- (superoxide), H_2O_2 (hydrogen peroxide), .OH (hydroxyl radical), ROOH (organic hydroperoxide), RO.(alkoxy radical), ROO.(peroxy radical), HOCl (hypochlorus acid)(7).The percentage of ROS increases during infection, exercises, exposure to pollutant light etc.

Table 1 Reactive species

Reactive Oxygen Species (ROS)	
Radicals	*Nonradicals*
Superoxide, $O_2^{\bullet -}$	Hydrogen peroxide, H_2O_2
Hydroxyl, $OH^{\bullet}$	Hypochlorous acid, HOCl
Peroxyl, $RO_2^{\bullet}$ (e.g. lipid peroxyl, see text)	Hypobromous acid, HOBr
	Ozone, O_3
Alkoxyl, $RO^{\bullet}$	Singlet oxygen $^1\Delta_g$
Hydroperoxyl $HO_2^{\bullet}$	
Reactive Nitrogen Species (RNS)	
Radicals	*Nonradicals*
Nitric oxide (nitrogen monoxide), $NO^{\bullet}$	Nitrous acid, HNO_2
Nitrogen dioxide, $NO_2^{\bullet}$	Nitrosyl cation, NO^+
	Nitroxyl anion, NO^-
	Dinitrogen tetroxide, N_2O_4
	Dinitrogen trioxide, N_2O_3
	Peroxynitrite, $ONOO^-$
	Peroxynitrous acid, ONOOH
	Nitronium (nitryl) cation, NO_2^+
	(e.g. as nitryl chloride, NO_2Cl)
	Alkyl peroxynitrites, ROONO

Figure 2

Free radicals can interact chemically with components of cells such as DNA,lipid, protein and take away their electrons in order to become stabilized. This in turn destabilizes the cell component molecules which then seek and accept electrons from another molecule that triggers a larged chain of free radicals action.

The mechanism of production of free radicals

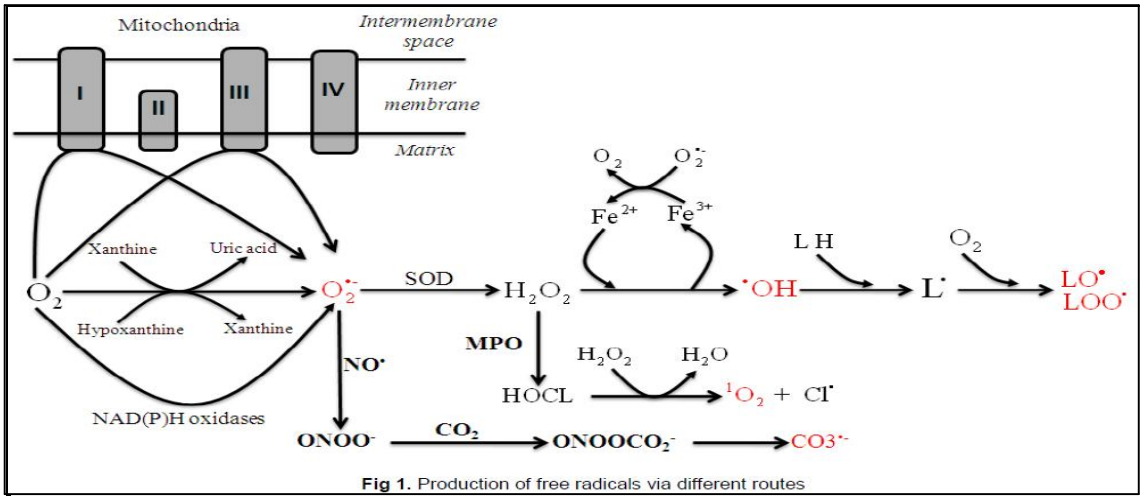

Figure 3

ROS also induced oxidative damage by producing different types of secondary radicals like lipid radicals, sugar, and base derived radicals, amino acid radicals and thiyl radicals. These radicals in presence of oxygen are converted to peroxy radicals which causes changes in the tertiary structure of protein, proteolytic degradation, protein-protein cross linkages and fragmentation. (8,9).Oxidative stress can be controlled by the depletion of free radicals. Damage of cells caused by free radicals can be protected by using antioxidants. The antioxidants are the compounds of either exogenous or endogenous in nature which can either prevent the generation of toxic oxidants or block the propagation of chain reaction of the free radicals produced by oxidants. The endogenous antioxidants can be classified as enzymatic (SOD, catalase, etc.) and non enzymatic. The non enzymatic antioxidants can be also divided into metabolic antioxidants (lipoic acid, uric acid, bilirubin,etc.) and nutrient antioxidants which belongs to exogenous antioxidants such as Vitamin E, Vitamin C, carotenoids, trace elements(Se,Cu, Zn, Mn).The nutrient antioxidants are supplied through diets as it cannot be produced in the body (10,11).

Several groups of evidence suggest a role for oxidative stress in the pathogenesis of Arthritis. Arthritis occurs due to diffuse inflammatory and degenerative lesion of joints. The knee is a hint joint formed by the meeting of the femur and the tibia. The knee joint is cushioned by articular cartilage that covers the end of the tibia and femur. The two main actions are flexion and extension with the ability to slightly rotate.(12) Changes of soft tissue causes swelling of joints, bone density is reduced by perarticular causing

inflammation, damage of the joint that is change of articular surface, narrowing of joint space indicates cartilage destructions, erosion (foci of subchondral bone destruction) causes Arthritis. Arthritis may also caused due to the alteration of the alignment of bones across a joint.(13) Cartilage damage occur due to excessive stress on a joint for a longer period of time. Cartilage damage is likely to occur mostly in the obese person than normal weight. This results in inflammation in joint known as osteoarthritis. Even if the joints are not moved for a longer period of time, it means if it remains inactive state there is an increase risk of cartilage damages. Damage of cartilage also occur if the joint receives a devastating impact, if someone have a back fall or automobile accident etc. the symptoms of cartilage damages is joint pain stiffness and swelling. This reflects the first clinical sign of Arthritis is a painful swollen joints (14).
The most important characteristic of toxic free radicals is peroxidation of lipids resulting in tissue damage and death of affected cells and main target of ROS attack are PUFA in the membrane lipids causing lipid peroxidation. The imbalance of free radicals play a role in tissue damage and inflammation process in Arthritis (15).

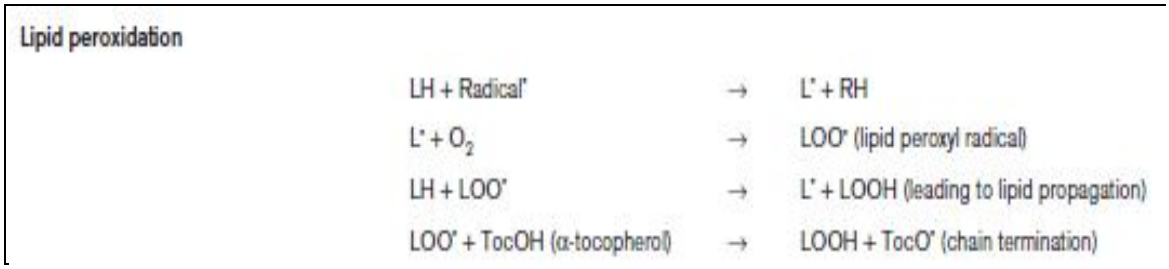

Figure 4

2. Health of the Joint Can Be Protected Through Diet

Dietary polyunsaturated fatty acid (PUFA) and certain plant derived phyto -chemicals such as flavonoid can reduce diet related chronic disease Arthritis. The level of antioxidant diminished due to the prevalence of environmental toxic such as heavy metals and organics. Since PUFA and flavonid has anti-inflamatory activities they reduces the inflammation in animals .Scientist at Perdue University focused on determining how candidate flavanoid and their metabolites affects gene target of inflammation in cell culture an animal model. Yong et.al introduce the concept for studying food components containing LC omega-3 PUFA and flavanoids that influence inflammation(16).Phytochemicals obtained from spices such as turmeric, red pepper, cloves, ginger, garlic, cumin, coumarin, anise, fennel, basil, rose mary, pomegranate, can interupt the pathway that activates nuclear transcription factor kappa B which is related to inflammatory disease Arthritis(17).It can also be treated with herbal medicines named Rosehip which has a specific anti-inflammatory action. Retention of phytochemical can be maximized by making a standardised rosehip powder. Red meat decreases the Antioxidant level. Processed and cooked meat contains hemichromes and hemocromes. After eating the meat heme protein is hydrolysed to amino acid and peptide. Heme group is coordinated to strong ligand and they are absorbed and transported to every tissues and organs by blood. Heme catalysed oxidation caused biochemical damage and hence increases oxidative stress. The decreased antioxidant level can be enhanced by taking vegetables fruits etc. Moreover, side effects of drugs, that are prescribed to reduce elevated oxidative stress, can be controlled by the intake of neutraceuticals(18,19,20)

3. Responsibility of Oxidative Stress in Arthritis

It is evident that oxidative stress that results due to the action mechanism of free radicals is mainly resposible for arthritis. Oxidative stress causes joint tissue damages. From the study of oxidative status by spectrophotometry or flow cytometry it is evident that the basal levels of ROS, superoxide, and hydroxyl ions enhance significantly in neutrophils from peripheral blood and synovial infiltrate. The generation of ROS and RNS (Reactive Nitrogen Species) causes oxidative or nitrative damage to proteins by overwhelming antioxidant defenses. By using zinc trap spectrophotometry high concentration of H_2S in Rheumatoid arthritis (RA), synovial fluid can be detected and the levels are correlated with clinical data of inflammation and disease activities (21). The level of lymphocytes DNA damages increases in the patients who are suffering from RA. In other words, damage in DNA increase oxidative stress and reduce antioxidant activities (22). Decrease in vitamin E and calcium/phosphorus ratio leads to the increasing generation of ROS that causes RA (23). Apart from this if the metabolism of collagen decreases it enhances the oxidative stress that mainly causes knee osteoarthritis (24). Osteoarthritis shows elevated level of oxidative stress markers 3-NT in the synovium. (25)

4. Role of Antioxidants in Arthritis

ROS is suppressed by CTLA 4 Ig fusion protein and prevent the synovial adherent cell induced in activation of Rap 1 (Rap belongs to RAS family)which is the GTPase mediator of oxidative stress in RA(26) by comparing Biological Antioxidant Potential (BAP) and Plasma Antioxidant Test (PAT) antioxidant capacity can be measured so that the oxidative stress can be reduced and hence Ra can be reduced(27).Bucillamine (BUC), a di-thiol compound, has antioxidant activities so it is useful for the treatment of RA. It can reduce stable free radicals by metal chelation rather than by scavenging free radical species (28). Phenolic antioxidants are produce by a metabolism that links proline synthesis through pentose phosphate pathway (PPP). Both PPP and stress induced proline biosynthesis drives synthesis of NADPH and sugar phosphate for anabolic pathway that includes oxidant response pathway (29). Barks of Pinus meritima (pycnogenol) contain poly phenol. It has free radicals scavenging capacity especially against ROS and NO. So regulation and generation of NO for human health is necessary by procyanidins extracted from pycnpgenol(30). Willow bark extracts posses anti- inflammatory action. It shows effects on COX1 and /or COZ enzyme as well as generation of free radicals (31). Atropa

acuminata posses antiinflammatory properties (32).Curcuminoids are poly phenolic phytochemicals that has anti-inflammatory properties and protective effects on chondrocytes so it can be used as a safe alternative tyreatment for osteoarthritis (33). Moreover, Dihydroorotate DeHydrogenase (huDHODH) is used as a therapeutic drug for RA. It can be inhibited by a synthetic inhibitor named Leflunomide. E-Pharmacophore are made on the basis of leflunomide and its act as a more efficient inhibitor than leflunomide(34).By measuring the level of lipid peroxidation (LPO) it is found that LPO increases in RA patient compare to that of OA(osteoarthritis) patients. On the other hand, total antioxidant capacity (TAC) is investigated and result is that with decrease in TAC level oxidative stress increases and causes RA (35). Hempseed rich in PUFA shows medical efficiency in RA for centuries. Investigations are made on the effect of hempseed oil (HO) on MH7A human RA fibroblast like synovial cells. HO reduces the survival rate of MH7A cell and promoted programmed cell death (apoptosis).Lipid accumulation of level of intracellular ROS increased in HO treated MH7A cell and it also exhibited increased expression of major endoplasmic reticulum(ER) stress marker, glucose regulated protein78 and C/EBP homologous protein (CHOP). CHOP act as an anti Rheumatoid factor downstream of HO in MH7A cell (36). But till now quercetin (a bioflavonoid) shows no effect on oxidative stress and inflammatory status of plasma and blood pressure in women with RA (37).

5. Regulation of Arthritis by Immune System

Inflammatory molecules monocyte chemotactic protein (MCP), Tumour necrosis factor-alpha (TNF-α), interleukin 1β (IL-1β) and interleukin 8 promote angiogenesis.MCP induced protein induced by MCP1, is also induced by other inflammatory agents. Oxidative stress was inhibited by apocynin or cerium oxide nanoparticles(38).MCP induced protein(MCPIP) expression induced oxidative stress result in endoplasmic reticulum stress leading to autophagy require for angiogenesis(39). Apart from this oxidative stress can be generated by the action of RAGE and causes RA(40).Various data suggest that T cell and Macrophage play a vital role in the initiation and perpetuation of synovial inflammation. TNF-α and IL-1β are mainly responsible for the elevated level of proinflammatory or inflammatory cytokines in RA(41). Generation of TNF-α by Macrophage, Mycroglial cell and Mast cell can be supressed by Flavanoids as a result RA will be improved. The inhibitory effect of flavonoids is due to the regulation of signalling pathway(42). Cytokines, interferons, endocrine hormones supressed nuclear factor –kappa B activation. It is a transcription factor that present in the cytoplasm of cell and translocates to the nucleous when activated. Its activation can be induced due to stress, cigarette smoking as a result it leads to RA(43). Smoking interact with HLA-DRBI shared epitope in the devolopment of ACPA (Anti-citrullinated protein antibody) which result in RA(44). Metalloproteinase, Disintegrin, Il-1β, Il-18, and TNF-α are the catabolic mediator of Osteoarthritis. Cellular changes occur not only in chondrocytes but also in macrophages (45).Within the cells of immune system ROS are considered to be an important signalling molecules. Due to the increased level of oxidative stress cells of immune system are exposed and as a result T cell becomes refractory to growth and death stimuli (46).

6. Biochemical Factors Influencing the Suppression of Arthritis

Co enzyme Q(10) supplementation capable to suppress inflammation and also play an important role to improve important marker of inflammation of oxidative stress(47). Gene alterration can also be a major pathogenetic mechanisms of osteoarthritis during OA cartilage degeneration. Mitochondrion plays an important role in OA as it is the important source of ROS. Moreover, oxidative stress can promote cell senescence and for this stress cell signalling pathway in chondrocyte can be altered that disrupts the response of growth (48).The result can be confirmed by immunohistochemistry for nitrotyrosine which is consider as a marker oxidant damage (49).Inducible nitric oxide synthase(iNOS) activity and it's inhibition can be characterised by assaying 3-nitro tyrosine(3NT) in an acute endotoxin challenge model of RA. Plasma level of 3NT are significantly elevated in the acute model of inflammation (50).Temporomandibular joint (TMJ) inflammation is associated with oxidative stress. N-acetyl cysteine(NAC) has antioxidant activity to compensate oxidative stress related damage in TMJ chondrocytes(51). We know, Antioxidant protects RA by combating oxidative stress but in case of women intake of antioxidant can't protect them from RA. It can be concluded by calculating 'ferric reducing ability of plasma' score (52).Moreover Thioredoxin (TRX) is a ubiquitous redox active protein which are secreted extracellularly and fight against oxidative stress. Level of plasma thioredoxin acts as marker for Oxidative stress in patients with RA. Plasma TRX level in patients with RA can be measured by ELISA and relationship to TRX concentration in inflammatory joints can be investigated (53).Oxidative stress in RA leukocytes are supressed by rutins and other antioxidants and chelators (54).Chronic inflammation of RA patients leads to cardiovascular disease beyond traditional cardiac risk factor(55).

7. Conclusion

Arthritis mainly occurs due to oxidative stress. Generations of free radicals cause oxidative stress.ROS and RNS are mainly responsible for oxidative stress. Arthritis mainly occurs when the antioxidant level is not equal to the level of ROS. Level of oxidative stress can be reduced by antioxidants. Apart from antioxidants,arthritis can be regulated by immune system and various biochemical factors.

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