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Review Article

Natural Therapies in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis is an autoimmune disorder that is categorized by systemic inflammation of synovial joints. There are various factors which are involve in the pathophysiology of RA, i.e. influx of B-cells, critical role of T-cells which initially attacks on synovial joints and many more. Oxygen metabolism generating Reactive Oxygen Species (ROS) and activating phagocytic cells plays an important role in the pathophysiology of RA. The progression cycle of oxidative reactions plays a significant role in case of RA. Reactive ions leads the cause include superoxide anions, hydrogen peroxide, hydroxyl radical, nitric oxide and hypochlorous acid. These ROS and RNS species setups repeated reactions disturbing the whole process of the immune system and genetic integrity causing RA. Thus, review about the detailed role of oxidant molecules involved in the pathophysiology of RA and the role of numerous antioxidants therapies to mitigate these stresses.

Keywords: Rheumatoid arthritis; Oxidative stress; Reactive oxygen species; Pathogenesis; Anti-oxidant; Vitamins

INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disorder which is characterized by systemic inflammation (rednesss, swelling, pain) of synovial joints and progressive attrition of cartilage and bones [1]. Synovial joint inflammation causes pain stiffness and eventually causes damage in joints which leads to deformities and breakdown of the body's functions. This process results in progressive bone and cartilage destruction causing enormous pain and disability specifically of small joints as hand feet and wrist [2,3]. Looking on the data of past many years it is found that around 60-120 million of the peoples were affected by this disease. Redistributing in terms of sex then it is found that women are more affected by this disease as compared to men [4]. Sign and symptoms of RA are fatigue, pain, tenderness, swelling, redness, warmth, stiffness of joints, loss of joint range of motion, limping, and joint deformity, and loss of joint function, anemia, fever, and depression. The pathogenesis of rheumatoid arthritis involves an immune imbalance of the endogenous system. Different type of causative factor involves immune imbalance, oxidative stress, genetic and environmental [5].

LITERATURE REVIEW

Pathophysiology of RA

There are various factors which are involve in the pathophysiology of RA, i.e. influx of B-cells, critical role of T-cells which initially attacks on synovial joints and many more. Below mentioned is the summary which explains the pathophysilogy of RA in a brief.

Critical role in the pathogenesis of RA is played by T-cell. The deep role root cause of T-cell is undefined however the patient with RA appears to have an access amount of T helper cell in synovial tissue. T-cells are found active in RA joints and these activated cell releases cytokines that stimulate cytotoxic cell and T-cell and other responsive cells. In the inflammatory site, neuropeptides are also released these neuropeptides plays an important role in activating macrophages and stimulates synovial fibroblast like cells to produce prostaglandins and metalloproteinases. Macrophages played an important role in the pathogenesis of RA through the released cytokines, interleukin-1 and tumour necrosis factor in the inflammatory process. The endothelial cell is also active in the inflammatory process in RA. They regulate coagulation exudation and fibrinolysis of fluid and solute from the vascular space and

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these play a critical role in the recruitment of inflammatory sites. The vasoactive substance also enhances release in the inflammatory process. Histamines kinins and prostaglandin release at the site of an inflammatory site increases blood flow at the site and also increases the permeability of blood vessels. This result is edema, erythema warmth and pain to the inflamed joint and also enables granulocytes in the blood vessel that reaches the site of inflammation

The Pathogenesis of RA has been initiated by the influx of lymphocytes as B-cell, CD4+ helper, CD8+ cytologic and T cell into the synovium.CD4+ cells are recognized antigens present into the joint and they stimulate plasma cells. Later Macrophages mast cell and synovial fibroblast initiate production of inflammatory mediators such as Tumour Necrosis Factor (TNF-a) and Interleukins (IL-1). These mediators stimulate the production of metalepsis that activates joint destruction. These synovial fibroblasts produce collagenases, induces cartilage resorption and osteoblast production increased expression of chemokines to adhesion and HLA molecules to stimulate an immune response [6].

In the pathogenesis of rheumatoid arthritis, oxygen metabolism plays an important role. In the course of cellular oxidative phosphorylation, Reactive Oxygen Species (ROS) and activated phagocytic cells during oxidative bursts exceed the physiological buffering capacity and result in oxidative stress). Excessive ROS produced can harm parts of proteins, lipids, nucleic acids, and matrix. They also serve as significant intracellular signaling molecules that amplify the inflammatory-proliferative reaction to the synovial reaction [7].

Role of oxidative stress in the pathogenesis of RA: Oxidative stress contains abnormal reactive oxidant generation, also known as Reactive Oxygen Species (ROS). These species are formed by the premature release of an electron through the mitochondria-based electron transport chain [8].

In the pathogenesis of rheumatoid arthritis, oxygen metabolism plays a significant role. In the course of cellular oxidative phosphorylation, Reactive Oxygen Species (ROS) activates phagocytic cells during oxidative bursts exceeding physiological buffering ability result in oxidative stress depicts the phagocytic cells like macrophages and neutrophils undergo an oxidative burst that produces highly toxic ROS to kill the invading pathogens. The NADPH oxidase system mediates oxidative burst, resulting in a marked rise in oxygen intake and superoxide anions output (O2-). NADPH consists of several subunits which fuse with intracellular phagocytic vesicles or the outer membrane at the plasma membrane. This enables the subsequently shaped focused release of oxidants. Superoxide is either spontaneously or more quickly transformed to hydrogen peroxide (H2O2) when catalyzed by superoxide dismutase, an enzyme that happens in two isoforms, one of which is induced by inflammatory cytokines such as tumor necrosis factor-α (TNF-α) [7]. Pathogenic cell leukocytes activate locally and generate ROS. Tissue injury releases iron and copper ions and heme proteins that are catalytic for free radical reactions. In the mitochondria and endoplasmic reticulum, electron transport chains are also interrupted, causing electrons to leak into superoxide (O_2^-). Increased production of ROS in RA patients was reported by increased concentrations of lipid peroxidation products [9]. Superoxide radical O2-, hydrogen peroxide (H2O2), hydroxyl radical (OH-), and Hypochlorous acid (HOCI) are the most significant Reactive Oxygen Species (ROS) involved in inflammatory tissue injuries. ROS can also occur through several methods in the inflamed joint. Oxidants can be generated in the synovial membrane by activated macrophages, chondrocytes and synovial cavity by activated neutrophils. The synovial cavity displays negative pressure and the vascular patenting is retained when the joint is exercised, enabling the nutrition of the avascular cartilage. The free radical mechanisms degradation of hyaluronic acid, Peripheral blood lymphocyte DNA from RA patients, considerably enhance the concentration of premutagenic 8-oxohydrodeoxyguanosine (8-oxodG), a product of oxidative DNA harm, indicating oxidative stress genotoxic impacts [10].

Due to free radical formation oxidation harms the biomolecules such as lipids, proteoglycans, DNA and proteins. Such damage can result in oxidation and instability of the membrane, irreversible changes in the protein. Mutagenesis and instability of DNA. Pathogenesis of many diseases including Alzheimer's disease, asthma, cardiovascular disease, and RA was thought to be associated with oxidative stress-mediated cellular damage. Despite the direct harmful effects of oxidative stress, it has become well accepted that oxidative stress also has more subtle effects on cellular function. It is now apparent in a mechanism commonly referred to as "redox signaling" that tightly controls homeostatic control of ROS/RNS impacts the activity of various intracellular molecules and signaling pathways [11].

Antioxidant treatment strategy

The body developed a series of defence mechanism in response to protect DNA from the free radical attack and its interferences with the normal physiology of the cell. Natural categories of anti-oxidant are vitamins, phytochemicalsand enzymes. In the condition of hypoxia (deficiency of oxygen) to mitochondrial respiration chain, generation of Nitric Oxidant (NO); peroxide (OONO) gives Reactive Nitric Species (RNS) [12]. Anti-oxidant act at different levels and by a different mechanism in the defence system such as by inhibition of oxidative mechanism, promoting radical scavenging, repair and adaptation. Distinctive defense line of antioxidant mitigating the oxidative stress and implementation of treatments has been deliberated further.

First line of defense: Naturally, the biological system produces antioxidant enzymes as an antioxidant mechanism for defence mechanism of the body against oxidative stress. The first line defence mechanism comprises the preventive oxidants which act by suppressing the formation of free radicals. The first line of defence mechanism includes Catalase (CAT), Glutathione Peroxide (GPx) and Superoxide Dismutase (SOD) which is examples of natural enzymatic oxidants. These antioxidants

prevent oxidative stress by suppressing the formation and scavenging of free radicals.

Second line of defence: Second line of defence includes retinol, α-tocopherol, uric acid, bilirubin, albumin and thiols. These anti-oxidant acts by scavenging active radicals, breaking the chain propagation reaction and suppression of chain initiation which helps in mitigation of oxidative stress.

Third line of defence: Third line of defence includes proteolytic enzymes, proteinases and peptidases which are present in the cytosols and in the mitochondria of mammalian cells, etc. They undertake the process of repairing deoxyribonucleic acid and thus, mitigating the oxidative stress.

Fourth line of defence: Fourth line of defence includes adaptation, in the signals for the production and reaction of free radicals induces the formation of antioxidants and transportation of the suitable antioxidant to the proper place.

Numerous types of natural antioxidants are found in nature which differs in their specifications along with the mechanism of action and their composition, etc. [13-17].

Treatment by anti-oxidant enzymes

These enzymes which act as an antioxidant are synthesized in the human body by utilizing the proteins and minerals consumed in daily diet. The examples of these enzymes are superoxide dismutase, glutathione peroxide, glutathione reductase and catalases. These enzymes require co-factors such as iron, copper, selenium, magnesium and zinc for anti-oxidant activity. These enzymes act by converting the reactive oxygen species and reactive nitrogen species into the stable compound and play an important in the repairing of damaged DNA, Proteins and oxidized peroxides. Some of the natural antioxidants which have been frequently used for the treatment of RA have been deliberated below.

Superoxide dismutase (SOD): Superoxide dismutase catalyzes the breakdown of superoxide anion into hydrogen peroxide and oxygen. Superoxide dismutase is present in aerobic cells as well as in extracellular fluids. In plants, superoxide dismutase is originated in chloroplast, peroxisomes and apoplast in the cytosol, while superoxide dismutase-1 are originated in cytoplasm and superoxide dismutase-2 in mitochondria and superoxide dismutase-3 in extracellular fluids in the human body [18-22]. The superoxide anion is converted into hydrogen peroxide in the presence of an antioxidant SOD enzyme, which in the presence of catalase enzymes degrades into non-toxic water and oxygen molecules [23]. Srivastava et al. reported that the enhanced ability of SOD to scavenge ROS produced by macrophages synovial RA fluid [24].

Catalase: Catalase enzyme purpose is to catalyze the decomposition of hydrogen peroxide into water and oxygen and it is an enzyme present in almost all living organism which is exposed to oxygen. The hydrogen peroxide is the harmful substance that is generated during various metabolic processes and to prevent damage from hydrogen peroxide, catalase converts the hydrogen peroxide into water and oxygen [25]. Surapuneni et al. reported the decreased levels of erythrocyte in GSH, ascorbic acid and plasma vitamin E (non-enzymatic antioxidant defence system) found in comparison to controls in patients with rheumatoid arthritis. The decrease in the levels of these non-enzymatic antioxidant parameters may be due to increased turn over, that indicates an increased defence against oxidant damage in rheumatoid arthritis to prevent oxidative damage in these patients [26].

Glutathione: Glutathione is a cysteine containing peptide found naturally in the aerobic organism and it is not required in the daily diet because it is synthesized in cells from amino acids [27]. The antioxidant activity is due to the thiol group in its cysteine moiety of glutathione. Glutathione is present in high concentration and one of the most important cellular antioxidant enzymes which play an important role in the maintenance of the redox state of the cell [28-34].

Hassan et al., reported that the impairment of antioxidant defence mechanisms against these oxygen free radicals. The GSH functions as an intracellular reductant in oxidation-reduction processes [35-42].

Delivery of antioxidant enzymes: Due to the fragile and sensitive nature of enzymes, the delivery of antioxidant enzymes is highly challenging for the researchers. Thus, several novel approaches have been pursued to deliver these enzymes [43-46]. Different novel approaches followed to enhance the efficacy of anti-oxidant delivery have been enlisted in Table 1.

Treatment by phytochemical

Phytochemicals are natural antioxidants that are produced and used by plants to protect against free radicals. Phytochemicals are naturally found in whole foods like whole grains, fruits and vegetables. Phytochemicals may be divided into the following categories.

Carotenoids eg: Lycopene, β-carotene, Leutein, Zeaxanthin.

Flavonoids eg: Quercetin, Genistein, Apigenin, Kaempferol.

Polyphenols eg: Caffeic acid, gallic acid, and ferulic acid.

Allyl sulphides eg: S-allylcysteine (SAC), S-allyl Mercaptocysteine (SAMC), Diallyl Sulfide (DAS), Diallyl Disulfide (DADS), and Diallyl Trisulfide (DATS).

Numerous phytochemicals used in the treatment of RA has been enlisted in Table 2.

Table 1: Series of antioxidants listed for therapy of RA.

S.No	Herbs	Mechanism of action	Remarks	References
1	Galangin	Anti-inflammatory herb suppresses signalling pathway by inhibiting NF-κB. Acts as an antagonist of the aryl hydrocarbon receptor induce apoptosis, inhibits cytochrome P450 isoform 1A1 with an IC50 value of less than 1 μM.	Inhibitors level of serum lysosomal enzyme and suppress the paw swelling.	[46]
2	Bergamot	Lipid-lowering effect was associated with significant reductions in biomarkers used to detect vascular oxidative damage (such as malondialdehyde, oxyLDL receptor LOX-1, and protein kinase B (PKB)), suggesting a multi-action improved potential for bergamot in patients taking statins.	Reduce the PEA-LUT formulation and that the effect of PEA along in reducing the inflammatory response is potentiated.	[47]
3	Oleuropein	Inhibits copper sulphate which induces oxidation of low-density lipoproteins (LDL).	They reduced activation of the nuclear enzyme(ADP-riboxyl) polymerase(PARP) involved in inflammation with a decrease in PAR expression in the inflamed joint.	[47]
4	Resveratrol	Resveratrol NF-kappaB (NF-kappaB) activation.	Reported to suppress the ROS production IL-1 synthesis, induces apoptosis and prostaglandin synthesis	[47]
5	Curcumin	Curcumin acts as a scavenger of oxygen species, such as hydroxyl radical, superoxide anion, and singlet oxygen and inhibits lipid peroxidation as well as peroxide-induced DNA damage 2.	Inhibits cyclooxygenase-2(COX-2) lipoxygenase, NF-αk inducible nitric oxide synthase and NO production.	[47]
6	Epigallocatechin-3-gallate	Inhibits growth of receptor phosphorylation, such as epidermal growth factor	ECG suppresses IL-1-induced glycosaminoglycan release from cartilage by blocking NF-kB activity in chondrocytes and inhibits cartilage degradation and IL-1-stimulated inducible nitric oxide synthase (iNOS)	[47]
7	Flavonoids	Flavonoids inhibit a number of enzymes such as aldose reductase, xanthine oxidase, phosphodiesterase, Ca(+2)-ATPase, lipoxygenase, cycloxygenase, etc. They also have a regulatory role in different hormones like estrogens, androgens and thyroid hormones.	They inhibit activities of many inflammatory proteins such as NF-kB and the expression of genes associated with chronic inflammatory disease	[47]
8	Piperine	Piperine inhibits the P-glycoprotein (P-gp)-mediated transport of drugs such as digoxin and cyclosporine A in Caco-2 cells (human colon carcinoma cell lines).	Reported to decrease arthritic symptoms in carrageenan induced acute paw arthritis.	[48]
9	Black cohosh	Oestrogen receptor modulator act as an antioxidant 2) through serotonergic pathways, 3) as an antioxidant, or 4) on inflammatory pathways.	Reported to decrease the inflammation produced due to arthritis.	[48]
10	Curcuminoids	Curcumin inhibits the STAT3 and NF-□B signalling pathways, which play keyroles in cancer development and progression.	They inhibited joint inflammation in both acute and chronic phases of arthritis.	[48]
11	Mangiferin	Inflammation, with respect to NF-κB, PPARγ and the immune system; (2) cell cycle, the MAPK pathway G2/M checkpoint; (3) proliferation and metastasis, and implications on β-catenin, MMPs, EMT, angiogenesis and tumour volume;	Reported to have anti-inflammatory activity.	[48]
12	Tinosporine	Tinospora cordifolia treatment decreases the concentrations of glutathione reductase.	It is used for the treatment of rheumatoid arthritis.	[48]
13	Superoxide Dismutase (SOD)	Superoxide dismutases (SODs) cases dismutation of superoxide anion free radical (O2-) into molecular oxygen and hydrogen peroxide (H2O2) and decrease O2-a level that damages the cells at excessive concentration.	SOD and Vitamin E have an anti-inflammatory role in experimentally induced arthritis.	[49]

14	Catalase	One hydrogen peroxide molecule oxidizes the haem to an oxyferryl species. In the second step, a second hydrogen peroxide molecule is used as a reductant to regenerate the enzyme, producing water and oxygen. Some catalases contain NADPH as a cofactor, which functions to prevent the formation of an inactive compound.	Reported an increase in plasma catalase activity in patients with rheumatoid arthritis.	[50]
15	Glutathione	Glyoxalase I catalyzes the conversion of methylglyoxal and reduces glutathione to S-D-Lactoyl-glutathione. Glyoxalase II catalyzes the conversion of S-D-Lactoyl Glutathione to Reduced Glutathione and D-lactate.	GPX is increased in group2 compared to group1. The levels of erythrocyte GSH, ascorbic acid, plasma vitamin E and Catalase activity was significantly decreased in patients with rheumatoid arthritis.	[50]
16	Ascorbic acid	Ascorbic acid is needed for collagen formation and tissue repair by acting as a cofactor in post-translation 4-hydroxyproline formation in -Xaa-Pro-Gly- collagen and other protein sequences. In the body, ascorbic acid is oxidized reversibly to dehydroascorbic acid.	Reported to increasesdefence againstoxidant damage in Rheumatoid Arthritis.	[50]

Table 2: Series of antioxidants listed for therapy of RA.

Antioxidant	Novel formulation	Activities	References
Superoxide dismutase (SOD)	Liposomes	Reported to enhance anti-inflammatory activity in an arthritis model.	[51]
Superoxide dismutase (SOD)	Liposomes and transferosomes	Moderation in inflammation.	[52]
Superoxide dismutase (SOD)	Liposome	Reported to have a moderating effect on the inflammation in RA.	[53]
Superoxide dismutase (SOD)	Liposome	Reported to have anti-oxidant and anti-inflammatory activity	[54]
Superoxide dismutase (SOD)	Transferosomes	Reported to have anti-inflammatory actives.	[55]
Catalase	Targeted by folate	Reported to moderating anti-oxidant and anti-inflammatory activities.	[24]
Catalase	Nanoparticle	Reported to have anti-inflammatory activities.	[56]
Glutathione	Liposome Nanoparticle Nano capsule	Reported to have to prevent the degradation of the therapeutic agent by increasing retention time and increasing tissue permeability.	[57]
Glutathione	PEGylated	Reported to have significance in the control of acuteepisodes of inflammation.	[58]

Anti-oxidant vitamins

The human body cannot naturally synthesize such antioxidant vitamins but are required to maintain good health and physiology, so we take these vitamins in our daily diet. Retinol, l-ascorbic acid, α-tocopherol, folic acid and beta-carotene are the examples of anti-oxidant vitamins. Retinol is imperative in tissue repair, for eye health, for improving the immune system as well as for improving cholesterol level. l-Ascorbic acid protects our skin from UV light damage and stimulates the immune system by providing resistance to infection and helps to control cholesterol levels.α-Tocopherol plays a significant role in maintaining healthy blood vessels and also improves the condition of the skin through cell membrane protection. Folic acid is useful in the process of erythropoiesis. Various phytochemicals such as carotenoids offer protection against singlet oxygen and free radicals. These carotenoids are found in orange vegetables such as carrots and dark green vegetables such as kale, etc.

High molecular weight compounds

The production of metal catalyzed free radicals is restricted by a few high molecular weight compounds like albumin, transferrin,

ceruplasmin, etc. [30]. Bergamol has shown a lipid-lowering effect with significant reductions in biomarker detection of vascular oxidative damage, indicating improved multi-action potentials of bergamote in patients taking statins.

Albumin: Albumin is the protein with the highest abundance and occupies over half the human plasma protein. It helps regulate several physiological processes such as providing colloidal osmotic pressure delivery, fatty acid solubilization, cell nutrient delivery and plasma pH balance. They have application in diabetes, hepatitis C and rheumatoid arthritis.

Transferrin: Transferrin, a micro heterogeneous iron-transporting N-glycoprotein, is used in the analysis of the glycosylation profile in rheumatoid arthritis [31].

Ceruplasmin: Ceruloplasmine is synthesized in the liver and recognized as the acute reactant and protein involved in the transport of copper and also is part of plasma protein 2-glycoprotein fraction. The antioxidant functions of ceruloplasmine are primarily linked to its activity of Ferroxidase I (FeOxI). FeOxI is responsible for converting reactive Fe^{2+} into Fe^{3+} (form bound in transferrin), thus preventing Fe^{2+} from taking part in hydroxyl radical generation.

Low molecular weight compound

Low molecular weight compounds like Tocopherol, quinines, bilirubin are lipid soluble antioxidants while ascorbic acid is water soluble antioxidants [32].

Minerals: Selenium, copper, manganese, and zinc is mineral antioxidants. Copper shows antioxidant activity through SOD while zinc is necessary for normal growth and reproduction of the body [33].

Vitamins: Vitamins are organic molecules and are essential for normal growth of the body which is helpful in maintaining normal physiology of the body. Retinol, ascorbic acid and tocopherol are popular antioxidant agent [34,35].

Ascorbic acid: The human body is not able to synthesize vitamin-C or l-ascorbic acid which is an antioxidant found in some animals and plants e.g., citrus fruits, so it is taken in food as a regular diet. Inside the cell, ascorbic acid is maintained in its reduced form by reacting with glutathione, which further catalyzed by protein disulfide, glutaredoxins and isomerase [36].Essentially vitamin-C is a reducing agent that can reduce, by neutralizing reactive oxygen species, such as hydrogen peroxide [37].

Tocopherol and tocotrienols: Vitamin E is a collective set of eight related tocopherol and tocotrienols, which is a fat soluble vitamin with antioxidant properties, and [38]. α-Tocopherol protects the cell membrane from oxidants by reacting with lipid radicals which are formed in the lipid peroxide chain [39]. These free radical intermediates are then removed and prevent the propagation reaction from continuing. In this reaction oxidized α-tocopherol radicals are formed which recycled back to the active reduced form through reduction reaction by other antioxidants such as vitamin-A, etc. [40].

Melatonin: Melatonin is produced by the pineal gland and has bleaching action on skin pigment i.e. melanin. Melatonin (N-acetyl-5-methoxytryptamine) is used as a protective agent against various processes and agents which damage the tissue via free radicals and is found in all living organism [41,42]. Due to its highly lipophilic nature melatonin have an ability to cross various barriers like cell membrane as well as highly selective barriers like BBB [43]. Melatonin also is known as 'suicidal anti-oxidant' because it cannot be recycled when it reduced to its former state [44].

External anti-oxidant: The human body is programmed to generate specific antioxidants to protect life but it is also designed to fight inflammation, disease and toxins naturally. In order to support such internal antioxidant systems, some external antioxidant in the diet has to be supplied on a regular basis. External antioxidant sources include vitamins and some specific food products, etc. Consumption of fresh fruits and vegetables on a regular basis can have a lower risk of health problems such as heart disease can also be prevented by taking tocopherol as a nutritional supplement [45-50].

CONCLUSION

The nutritional supplement includes specific antioxidant chemicals like polyphenol, resveratrol and some other minerals and vitamins. Spices like turmeric, coriander, cumin, and fennel also have medicinal properties. Food and part of foods that provide medicinal benefits are known as "Nutraceuticals". These neutraceuticals were also helpful in maintaining the normal physiology of the body.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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