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ROLE OF FENTON REACTION IN THE PATHOGENESIS OF VATAVYADHI-CONCEPTUAL STUDY

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ABSTRACT

In Ayurveda, *Vatavyadhi* represents a vast spectrum of eighty or more neurological and musculoskeletal disorders caused by the vitiation of *Vata dosha*. Modern medicine identifies oxidative stress specifically the production of highly reactive hydroxyl radicals via the Fenton reaction as a primary driver of similar degenerative and inflammatory pathologies. **Objective:** This review aims to bridge Ayurvedic pathology with contemporary biochemistry by analyzing how the Fenton reaction and its lipid peroxidation by-products, Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE), correlate with the two primary mechanisms of *Vatavyadhi*: *Dhatukshaya* (tissue depletion) and *Margavarodha* (pathological obstruction). **Methodology:** A conceptual integrative approach was conducted using classical Ayurvedic texts (*Charaka Samhita*, *Ashtanga Hridaya*) and modern biomedical literature focusing on Reactive Oxygen Species (ROS) and transition metal catalysis. **Results:** Dhatukshayajanya Vatavyadhi correlates with MDA-mediated lipid peroxidation. The loss of *Snigdha guna* (unctuousness/lipids) and subsequent tissue atrophy mirrors the destruction of membrane polyunsaturated fatty acids (PUFAs). Margavarodhajanya Vatavyadhi correlates with 4-HNE-mediated signaling. The

accumulation of morbid tissues (*Kapha*, *Pitta*, *Ama*) creates an inflammatory environment that generates 4-HNE, leading to protein adducts that obstruct cellular signal transduction, mirroring the Ayurvedic concept of *Avarana*. **Conclusion:** The Fenton reaction serves as a unifying biochemical initiator for *Vatavyadhi*. Understanding these molecular pathways provides a scientific basis for the degenerative and obstructive manifestations of *Vata* disorders, potentially guiding more targeted integrative therapeutic approaches.

KEYWORDS: oxidative stress, lipid peroxidation, 4-HNE, MDA, Fenton reaction, *Dhatukshaya*, *Margavarodha.*

INTRODUCTION

Vata vyadhi is a comprehensive clinical category in classical Ayurveda, encompassing all diseases primarily attributed to the vitiation of *Vata dosha* one among the *Tridosha* that govern all physiological processes. The concept of *Vatavyadhi* is not limited to a single disease entity but represents a spectrum of eighty or more conditions ranging from neurodegenerative disorders to musculoskeletal derangements. The *Vata* when unvitiated or in normal state sustains all systems and organs. It has five forms i.e. *Prăna, Udana, Samana, Vyana and Apana* initiates all actions i.e. upwards and downwards movements; it controls and also impels the mind. It stimulates all sense organs for quick actions, and carries all sense objects causes structural formation of all *dhatus*, it stimulates *agni* absorbs *doṣas*, expels out *malas*, makes major and minor most or subtle channels, gives the shape to the fetus and maintains life span.[1] The *hetu* for vitiation of *vata doshas* can be divided into two main types i.e. *Dhatukshayajanya* and *Margavrodhjanya*.[2] *Vata vyadhi* is considered as one among the Maharoga among the 8 *Maharogas* those which are difficult to treat according to Acharya Vagbhata.[3] All types of *vata vyadhi* are having the following natural inherent qualities(*atmarupas)* and actions wholly and partially. The qualities are *Raukshya* (roughness), *Saithya* (coolness), *Laghu* (lightness), *Vaisadya* (non-sliminess), *Gati* (movement), *Amurtatva* (shapeless) and *Anavasthitatva* (instability). The *Vata* which is having these inherent properties transmit in different parts of body and leading to following actions they are *Sramsa* (looseness), *Bhramsa* (dislocation), *Vyasa* (expansion), *Sanga* (obstruction), *Bheda* (separation), *Sada* (depression), *Harsha* (excitation), *Tarsa* (desire), *Kampa* (tremors), *Varta* (circular movements), *Cala* (vibration), *Toda* (piercing pain), *Vyatha* (aching), *Khara* (coarseness), *Parusha* (roughness), *Vishadha* (non-sliminess), *Sushira* (porousness), *Arunavarna* (reddishness), *Kashaya virasa mukha* (astringent taste in the

mouth), *Sosa* (wasting), *Sula* (colic), *Supti* (numbness), *Sankoca* (contraction), *Stambha* (rigidity) and *Khanja* (lameness) these are the Atmarupas of Vata.[3] Where the general treatment for *Vata* includes drugs having *madhura, amla, lavana, snigda* and *ushna gunas* and also therapeutic procedures like *Sneha, sweda, Anuvasana basti, Asthapana basti, Nasya karma, Abhyanga, Utsadana, Pariseka etc.*[4]

In contemporary biomedical science, Oxidative stress is a state of disturbed balance between the production of reactive oxygen species (ROS) and the efficiency of antioxidants.[5] The pathological imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms — has emerged as a unifying molecular mechanism in the pathogenesis of ageing, neurodegeneration, diabetes mellitus, cardiovascular disease, and cancer. Among ROS-generating pathways, the Fenton reaction plays a central role in producing hydroxyl radicals (•OH), one of the most reactive and cytotoxic free radicals in biological systems. Reactive Oxygen Species (ROS) are a natural byproduct of oxygen metabolism. At physiological consequence of incomplete reduction of molecular oxygen, which results in generation of superoxide anions (O2−), hydrogen peroxide (H2O2), highly reactive hydroxyl radicals (OH°) and hydroxide ions (OH−). At physiological levels, ROS regulate multiple cellular processes like proliferation, migration, and differentiation. However, increased levels of ROS are associated with pathological conditions, such as cancers, neurodegeneration, aging, and vascular calcification.[6]

Understanding the vata vyadhi from the basics of Fenton reaction helps us to know the insights to understand the diseases and generation of hydroxyl radicals which are most reactive free radicals and are capable of causing severe damage to biological molecules. Considering the degenerative nature if Vatavyadhi, oxidative stress mediated by Fenton reaction may provide a biochemical explanation for certain pathological processes described in Ayurveda.

MATERIALS AND METHOD

This is a conceptual integrative study. Sources included Classical Ayurvedic references on *Vatavyadhi* from Charaka Samhita and Ashtanga Hridaya. Modern biomedical literature describing Fenton reaction and ROS generation. Studies detailing lipid peroxidation and biomarkers such as MDA and 4-HNE.Comparative analysis was conducted to identify parallels between oxidative stress–induced degeneration and Ayurvedic descriptions of *Vata* aggravation and *Dhatu* depletion.

RESULT AND DISCUSSION

1. Fenton reaction and hydroxyl radical formation.

Fenton reaction is a chemical reaction in which ferrous iron reacts with hydrogen peroxide (H2O2) to produce highly reactive hydroxyl radicals (OH). These Hydroxyl radicals attack polyunsaturated fatty acids in cell membranes; they trigger lipid peroxidation this process generates toxic aldehyde by-products such as 4 HNE (4-Hydroxynonenal) and MDA (Malondialdehyde).

Primary Fenton Reaction

The Fenton reaction was first characterised by Henry John Horstman Fenton in 1894, who observed the catalytic oxidation of tartaric acid by hydrogen peroxide in the presence of ferrous iron.[7] The reaction proceeds as follows.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^- \quad \text{..... (Reaction 1)}$$

The ferric iron (Fe^{3+}) produced can be reduced back to ferrous iron via the Haber-Weiss reaction:

$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2 \quad \text{..... (Reaction 2)}$$

The net Haber-Weiss reaction, catalysed by iron, combines Reactions 1 and 2.

$$O_2^- + H_2O_2 \xrightarrow{ae} O_2 + OH^- + \bullet OH \quad \text{... (Net Haber-Weiss)}$$

Fenton-Like Reactions

Beyond the primary reaction, Fenton-like reactions involve iron (II) complexes with organic ligands (L) and other transition metals (copper, manganese, chromium), all generating •OH via the following generalised mechanism.[7,8]

$$M^{n+} + H_2O_2 \rightarrow M^{n++1} + \bullet OH + OH^- \quad \text{... (Fenton-like)}$$

These reactions are particularly relevant to biological systems given the ubiquity of transition metals in metabolic pathways and the ready availability of H_2O_2 as a metabolic by-product of mitochondrial respiration and peroxisomal β-oxidation.[6]

The hydroxyl radical can be generated by the Fenton reaction which was named after the discoverer of the catalytic oxidation of tartaric acid by H2O2 in the presence of iron (II). It

can also be produced from reactions of iron (II) complexes with a ligand (L) and other transition metal complexes with H2O2, called Fenton-like reactions.[9,10]

The Fenton reaction is a catalytic process where iron salts react with hydrogen peroxide (H_2O_2) to generate the highly reactive hydroxyl radical (.OH).
The resulting hydroxyl radical is the most reactive oxygen species (ROS) known, capable of damaging almost every molecule in a living cell.

The •OH radical is the most reactive species in the ROS spectrum, with a half-life of approximately 10^{-10} seconds and a rate constant of approximately 10^{9-10} $M^{-1}s^{-1}$ with most biological molecules. Unlike superoxide ($O_2•^-$) and hydrogen peroxide (H_2O_2), •OH cannot be enzymatically neutralised — it reacts indiscriminately with the first biological molecule it encounters. Specific targets include: DNA (strand breaks, base modifications) proteins (carbonylation, nitrosylation); and membrane phospholipids (initiating lipid peroxidation chain reactions).[8,11]

2. Lipid peroxidation mechanism.

Lipid peroxidation can be described generally as a process under which oxidants such as free radicals or non-radical species attack lipids containing carbon-carbon double bond (s), especially polyunsaturated fatty acids (PUFAs) that involve hydrogen abstraction from a carbon, with oxygen insertion. The overall process of lipid peroxidation consists of three steps: initiation, propagation, and termination.

i. Initiation: Hydroyxl radical abstracts a hydrogen atom from a bis-allylic carbon of a PUFA, generating a carbon-centred lipid radical (L•) and water. Lipid radical rapidly undergoes molecular rearrangement to form a conjugated diene.
ii. Propagation: lipid radical reacts with molecular oxygen (O_2) to form a lipid peroxyl radical (LOO•), which abstracts hydrogen from an adjacent PUFA membrane lipid, yielding a lipid hydroperoxide (LOOH) and a new Lipid radical. This chain reaction propagates until termination.
iii. Termination: Chain termination occurs when two radicals react with each other to form non-radical products, or when α-tocopherol (Vitamin E) donates a hydrogen atom to lipid peroxyl radical, generating a toco pheroxyl radical that is subsequently reduced by ascorbate (Vitamin C).

Lipid peroxidation of oxygen with unsaturated lipids produces a wide variety of oxidation products. The main primary products of lipid peroxidation are lipid hydroperoxides (LOOH). Among the many different aldehydes which can be formed as secondary products during lipid peroxidation, malondialdehyde (MDA), propanol, hexanal, and 4-hydroxynonenal (4 HNE). MDA appears to be the most mutagenic product of lipid peroxidation, whereas 4-HNE is the most toxic.[12,13]

3. Role of MDA in Vatavyadhi

Malondialdehyde (MDA) is a highly reactive organic compound and a key biomarker of oxidative stress, produced when free radicals attack polyunsaturated fatty acids (lipid peroxidation). It causes, cytotoxic and mutagenic effects by damaging DNA and proteins. Elevated MDA levels are associated with aging, atherosclerosis, and neurodegenerative diseases. MDA has been widely used for many years as a convenient biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids because of its facile reaction with Thiobarbituric acid (TBA).

Tissue-depleting states are associated with reduced tissue pH (acidic microenvironment), increased iron mobilisation from ferritin stores, and reduced antioxidant reserves — collectively potentiating Fenton reaction activity. The resultant •OH generation propagates lipid peroxidation, consuming membrane PUFAs and generating MDA. Loss of the lipid-rich snigdha guna creates desiccation and atrophy of tissues.

MDA can be correlated to *Dhatukshayaja Vata vyadhi* where due to Dhatukshayajanya Hetu there will be decease in PH level and acidic involvement is more leading to fenton reaction and free radicle release that which react with Hydrogen peroxide release the hydroxyl radical leading to Dangerous ROS (Reactive Oxygen Spices) and *snehadi guna snunya* (lipid peroxidation) or drying of Sneha leading to *Dhatu kshayaja Vata vyadhi.*

Sandhi saithilya is observed when the *shelshma bhava* declines along with the *shleshaka kapha* in the joints. *Ashrayashrayi sambandha* causes *Asthidhatu kshaya* results in *Khavaigunya* in the joints.[14] Structural disintegration vacates the *srotas* (body channels), which are then occupied by aggravated, unrooted *Vata.* With vacant *srotas* and depleted structural tissues, *Vata* produces increased and erratic activity manifesting as tremors *(Kampa),* numbness *(Supti),* atrophy *(Sosa),* and hyperalgesia the hallmark clinical picture of *Dhatukshayajanya Vatavyadhi occurence* of *Vata vyadhi*.

MDA in Disease

Elevated serum and tissue MDA levels have been documented in: Alzheimer's disease and other neurodegenerative conditions,[15] type 2 diabetes mellitus and diabetic neuropathy[16] rheumatoid arthritis and osteoarthritis (conditions with significant musculoskeletal overlap with *Vatavyadhi*[17] atherosclerosis and coronary artery disease; and healthy ageing. To treat *Dhatukshayajanya Vatavyadhi* is to control the vitiation of *vata* and correct the destruction of Dhatus.

4. Role of 4-HNE(4-Hydroxynonenal) in Vata vyadhi

4-Hydroxynoenal(4-HNE) is considered as major, highly reactive aldehyde product formed during lipid peroxidation[17] and one of the mediators of Oxidative stress in cells and tissue. 4-HNE frequently used as an oxidative stress marker, can be used with oxysterols to assess oxidative stress, and has been associated with the pathogenesis of cancer, neurodegenerative diseases, diabetes, and other diseases. Where, there will be Avarana of Mamsa, Medha, Raktha leading Avarana janya vyadhis.

4-HNE can be correlated to *Margaavaranajanya Vata Vyadhi*, When *Margavarodhajanya hetu* are operative — accumulation of Kapha, Pitta, or morbid Ama within the srotas — the resultant obstruction creates an inflammatory, lipid-laden microenvironment within and around body channels. This precisely parallels the conditions that favour 4-HNE generation: omega-6 PUFA–rich membrane environments subjected to inflammatory ROS.

The obstructing *doshas (Mamsa, Meda, Raktha)* generate localised oxidative stress through inflammatory cell activation, transition metal release, and mitochondrial dysfunction. 4-HNE formation impairs membrane receptor function and ion channel activity in neural and vascular tissues, creating protein adducts that obstruct normal signal transduction — biochemically mirroring *Avarana*. Due to *Margavarodha, prakupitta vata* begins to move throughout the body.

Obstructed srotas trap or suppress normal Vata movement, producing decreased or absent functioning in the affected channels. This manifests clinically as spasticity, compressive neuropathy, obstructive pain *(Sula),* and sensory loss — the defining presentation of *Margavarodhajanya Vatavyadhi.*

where there is *avarana* of *Mamsa, Medha* and *Raktha* there will be decease in PH level and acidic involvement is more leading to Fenton reaction and free radicle release that which react with Hydrogen peroxide release the hydroxyl radical leading to Dangerous ROS (Reactive Oxygen Spices) leading to *Avarana Janya Vata vyadhi*.

The Srotas are surrounded or hindered by the other doshas which have accumulated in the srotas and producing decreased or loss of functioning in the srotas. Here, along with vata there is the association of other doshas and dhatu leading to Avarana and occurrence of Vata vyadhi.

4-HNE in Disease

4-HNE has been identified as a major pathological mediator in: Alzheimer's disease (4-HNE adducts on tau protein and amyloid precursor protein) Parkinson's disease (4-HNE modification of α-synuclein and mitochondrial complex I proteins).[14] diabetic neuropathy; non-alcoholic steatohepatitis (NASH), inflammatory bowel disease, and atherosclerosis. It activates multiple inflammatory signalling pathways, promoting both pro- and anti-inflammatory responses depending on cellular context and concentration. Removing obstructions and reorienting the *vata* flow are two ways to treat *Margavarodhajanya vatavyadhi.*

CONCLUSION

This conceptual integrative study demonstrates a mechanistically coherent correlation between the classical Ayurvedic framework of *Vatavyadhi* and contemporary biomedical understanding of Fenton reaction–mediated oxidative stress. The generation of hydroxyl radicals via the Fenton pathway, subsequent lipid peroxidation, and the differential production of MDA and 4-HNE collectively explain the molecular basis of tissue degeneration, desiccation, structural disintegration, and functional loss described in *Vatavyadhi* pathology. In *Dhatukshayajanya* disease, tissue depletion and the progressive loss of lipid integrity (snigdha guna) directly parallel MDA-mediated phospholipid degradation, as seen in atrophic, degenerative, and demyelinating neuro-musculoskeletal conditions. In *Margavarodhajanya* disease, the accumulation of morbid tissue within channels parallels 4-HNE-mediated inflammatory and apoptotic signalling, consistent with compressive and obstructive neuropathies, spastic conditions, and inflammatory joint disease. Critically the Fenton reaction serves as the common initiating biochemical event in both pathways.

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