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# Curcumin Lozenges as an Adjunct to SRP and Its Effects on Oxidative Stress Markers.

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## Introduction

Periodontitis is an multifactorial disease initiated by the subgingival biofilm and modified by the individual's anomalous immune response. There is a strong notion that oxidative stress also plays an important role in the progression of Periodontitis (1). Oxidative stress is caused by an imbalance between excessive ROS production and anti-oxidant mechanisms. Reactive oxygen species (ROS) including the superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), and hydroxyl radicals ($OH^·$)

are byproducts of aerobic metabolism . Reactive oxygen species are actively involved in cell signaling and metabolic processes they are also actively involved in protective mechanism against diseases associated with phagocytic infiltration (host bacteria interaction). Excessively produced ROS molecules are proficient enough to cause changes in DNA, lipids and proteins that contribute to tissue damage (2).

Antioxidants are coumpounds that play major role in preventing the damage caused by the overproduction of ROS,by ensuring the maintenance of balance between oxidant and antioxidant mechanism. Antioxidants can be classified into different types by their activity they can be classified into enzymatic and non enzymatic antioxidants. Based on their mode of action into Preventive antioxidants and Scavenging. The enzymeatic antioxidants such as GPx, CAT, and SOD catalyze reactions to neutralize free radicals and ROS by forming a defense mechanism to

protect the cell . SOD is found in all the tissues and cells of aerobic organisms. There are three types of SODs in mammals, namely the cytosolic Cu Zn SOD, mitochondrial Mn-SOD, and extracellular Cu Zn SOD. SOD is a key antioxidant enzyme that efficiently and specifically scavenges superoxide anion ($O_2^-$) by catalyzing its dismutation to $H_2O_2$ and $O_2$ (3).

GSH is a main ubiquitous selenoperoxidase present in most cells; found in the cytosolic and mitochondrial compartments. It is an important antioxidant enzyme that catalyses the detoxification of $H_2O_2$ and lipid hydroperoxides and preventing damage to the cells and tissues (4).

The use of antioxidants in treating periodontal disease has gained importance in the recent years. These Antioxidants can be used to treat periodontal disease locally or systemically. This lead to the introduction of various commercially available antioxidant supplements.

BUT, Ancient natural medicinal plant and its products have been used as a traditional treatment agent for numerous human diseases throughout human history for various purposes. One such important natural medicial plant is TURMERIC. Turmeric is a plant that widely cultivated in the tropics and goes by different names in different countries. In North India, turmeric is commonly called “haldi,” and in the south it is called “manjal,” a word that is frequently used in ancient Tamil literature and has a very long history of medicinal use, dating back nearly 4000 years. Turmeric is used not only as a principal spice in cooking throughout Asia but also as a sacred component in religious ceremonies and rituals. Turmeric is also known as “Indian saffron.” because of its bright yellow color (5).

Curcumin, a polyphenol, a symmetric molecule, also known as diferuloyl methane is extracted from the turmeric plant. The IUPAC name of curcumin is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, with chemical formula C21H20O6, and molecular weight of 368.38. The chemical structure of curcumin has two aromatic ring systems containing o-methoxy phenolic groups, connected by a seven carbon linker consisting of an α,β-unsaturated β-diketone moiety (6).

Curcumin has a wide range of therapeutic effects like Anti-inflammatory, Antimicrobial, Antiplatelet aggregation, Antimutagenic and Antioxidant effects. Out of all the effects their antioxidant property is highly significant thus this study mainly focuses on the antioxidant property of curcumin (7). Curcumin consumption has shown to improve many important systemic markers of oxidative stress such as superoxide dismutase (SOD), glutathione peroxidase (GSH), Malondialdehyde (MDA) (8).

Lozenges are small sweetened and flavored medicated material that is designed to be held in the mouth for slow dissolution. TURMA NOVA a curcumin lozenges is currently the only commercially available curcumin containing lozenges. The aim of the present study was to find the effectivenss of curcumin lozenges on oxidative stress biomarkers such as SOD and Glutathione Peroxidase and as an adjunct to non surgical Periodontal therapy (SRP).


Figure 1

**Materials and Methods**

This study was conducted in the Department of Periodontics at Thai Moogambigai dental college and hospital Chennai Tamil Nadu after the protocol was ethically approved by the Institutions Committee for Research and Ethics by D.R MGR Educational and Research Institute. All the patients were informed about the study and their informed consent was obtained. Twenty subjects with Periodontitis (10 males and 10 females) were selected each having more than 20 remaining teeth with more than six sites with >4 mm PD, ≥3 mm CAL; and radiographic evidence of alveolar bone loss where included and divided into two groups (10 subjects in each group). Group I consisted of subject with Periodontitis for which only non surgical periodontal therapy was performed, where as Group II consisted of subjects with Periodntitis for which a combination of non surgical periodontal therapy and CURCUMIN LOZENGES supplements were given and were instructed to take 2 lozenges per day from day one after the SRP till day 50.

All subjects in the study were systemically healthy and had no periodontal treatment or surgery was done in the past six months. Patients on Antibiotic use or periodontal therapy, Systemic diseases, Orthodontic therapy, Pregnant women and lactating women were excluded from the study.

The clinical periodontal examination was performed by a single examiner and the parameters such as plaque index (PI), bleeding on probing index (BPI), periodontal pocket depth (PPD), and clinical attachment level (CAL), were measured at the mesial, distal, buccal, and lingual aspects of each tooth was measured. Both the parameters were examined on day one and on day 50 in both the groups.

After the sampling process, full-mouth clinical measurements including all the clinical parameters mentioned above were performed and recorded into the patient's case sheet. The Non-surgical periodontal treatment protocol included oral hygiene instructions and full-mouth scaling and root planing. Both the treatment was performed by the same periodontist under local anesthesia. The subjects were recalled for regular follow up and on day 50 the samples were collected again.

Both GSH and SOD were measured from the GCF samples. First the area was isolated with cotton rolls to eliminate any salivary contamination, and the site was gently air dried and GCF was collected from the sites with deep pockets using capillary tube method. Any capillary tube that was contaminated with blood was discarded and the collection process was repeated in that particular site.

The collected samples were stored in a epenndoff container with phosphate buffer saline solution at – 80'c till analyses. Superoxide dismutase activity was analysed spectrophotometrically and the data was noted in u/mg/mol proteins. Glutathione peroxidase was also analysed spectrophotometrically using recycling enzymatic assay and the data was recorded in mg proteins.

**Statistical analysis**

All the statistical analyses were performed using SPSS and the Student t-test was used to explore the differences between the two study groups and was found to be statistically significant at $P < 0.05$.

**Results**

There was a significant difference in the SOD and GSH levels in **GROUP II** compared to GROUP I. There was a significant difference in clinical paramenters between the base line and after 50 days results of both GCF and GSH levels in Group II compared to Group I (TABLE I), Also there wasn't any significant difference in Group I baseline vs 50 days comparision.

Table I: Clinical Parameters of Group I

| Clinical Parameter | Base Line | 50 Th Day | P Value |
|---|---|---|---|
| Probing Depth | 5.42+-0.441 | 5.13+-0.491 | <0.001 |
| Clinical Attachment Loss | 5.37+-0.17 | 5.15+-0.45 | <0.001 |
| Bleeding On Probing | 2.8+- 0.3 | 1.2+- 0.4 | <0.001 |

All p value significant at <0.05

Table II: Clinical Parameters of Group II

| Clinical Parameters | Base Line | 50 Th Day | P Value |
|---|---|---|---|
| Probing Depth | 5.09+-0.592 | 4.60+-0.49 | <0.001 |
| Clinical Attachment Loss | 5.04+-0.499 | 4.43+-0.39 | <0.001 |
| Bleeding on Probing | 2.8+-0.4 | 1.2+-0.3 | <0.001 |

All p value significant at <0.05

Table III: Oxidative Stress Marker Sod in Group I & II

Super Oxide Dismutase

In GCF U/Min/mg Proteins

| SOD | Base Line | 50 Th Day | P Value |
|---|---|---|---|
| GROUP I | 0.911+-0.202 | 0.89+-0.242 | <0.001 |
| GROUP II | 1.194+-0.280 | 1.505+-0.304 | <0.001 |

Table IV: Oxidatives Stress Marker Gsh In Group I & II

Gluthatione Peroxidase

IN GCF mol/Min/mg proteins

| GSH | Base Line | 50 Th Day | P Value |
|---|---|---|---|
| GROUP I | 0.71+-O.104 | 0.74+-0.101 | <0.001 |
| GROUP II | 0.779+-0.096 | 0.874+-0.070 | <0.001 |

All p value significant at <0.05

**Discussion**

Periodontitis is an inflammatory disease, which is initiated by bacterial infection and ensuing by aberrant host response. Pathogenesis of periodontal destruction starts with polymorphonuclear leukocytes (PMN) which act as the primary mediators of the host response against periodontal pathogens. Activated PMN produce a large amount of reactive oxygen species (ROS) and thus destruction of periodontal tissues follows (9).

Reactive oxygen species (ROS) are poly unsaturated fatty acids (PUFA) that are involved in normal cellular metabolism and continuously generated by the cells in most tissues. Under physiological conditions, ROS are effectively neutralized by antioxidants, which prevent ROS-mediated tissue damage (10). When inflammation happens, ROS production is drastically increased mainly due to cells of innate immune system, e.g., neutrophils and macrophages during the process of phagocytosis via the metabolic pathway of the “respiratory burst” (11).

Respiratory burst (RB) is a process in which there is rapid increase in the production of reactive oxygen species (ROS) during the phagocytosis . RB is an double edged sword it has an essential component of innate immunity in which they enable the phagocytic cells to eliminate microbes, at the same time excessive production of ROS may result in the formation of oxidative stress in cells (12).

The reactive oxygen species and antioxidants exist in zestful stability in a given normal physiology. Oxidative stress occurs only when there is a shift in this normal physiology thus we can define Oxidative stress as an imbalance of free radicals and antioxidants, which can lead to cell and tissue damage. This is characterized by increased metabolites of lipid peroxidation, DNA damage and protein damage (13).

Anti oxidants are the major compounds that inhibit oxidation by breaking the chain reaction that causes cellular damage. Anti oxidants are of two groups one is preventing anti oxidants and the other is scavenging antioxidants. Preventing antioxidants consists of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase. Scavenging antioxidants consists of ascorbic acid (vitamin C), carotenoids (including retinol-vitamin A), uric acid, α-tocopherol (vitamin E), reduced glutathione, and polyphenols (flavenoids) (14).

Superoxide dismutase is an excellent biochemical marker for oxidative stress, it is an metalloenzyme (metal ion containing enzyme that have the ability to directly bind to protein) whose primary function is to act as first line defence against ROS and responsible for the disproportionation of superoxide to molecular oxygen,

hydrogen peroxide and decrease $O_2^-$ level in the cells. With inflammation and age SOD level drops down naturally, which is one of the important reason for the hype and incorporation of SOD therapeutically world wide.

Glutathione peroxidase (GPx) is an intracellular antioxidant that is widely present in the cytosol of the cells. Glutathione peroxidase (GPx) family is classified according to the location of their isozyme encoding by different genes which makes them more specific to cell type. GPx1 is widely abundant compared to the rest of the family and is a very potential antioxidant. GPx2 is present in the intestinal cells, GPx3,4&5 are seen in lipids and plasma and GPx6 is seen in olfactory cells. Glutathione peroxidase-1 (GPx-1) helps in preventing the accumulation of hydroperoxidase and catalyses the detoxification of $H_2O_2$ and lipid peroxides. GPx1 is now beign uses as an potential therapeutic agent as they help in the development and prevention of many common and complex diseases, including cancer and cardiovascular disease.

Curcumin a biologically active component of turmeric is an well known food and pharmacological agent that's popular for its extensive medicinal properties in respect to both ancient and new age medicine. Turmeric has more of a cultural value in Asian countries, they form the root of many vedic and religious practices and ceremonies in these Asian countries. Curcumin is humbly known for many of its valuable properties like antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties. Over the century their antioxidant capacity has been much explored by researchers, and has been concluded as an potent antioxidant already. But there isn't any study prior to this elaborating about the properties of curcumin in an LOZENGES form, these are much tolerated by any age group of people as lozenges are sweetend and easy to consume when compared to other conventional modes in which turmeric is consumed, which is said to have an mild bitter taste.

In a study conducted by Tuba EK et al Curcumin was found to be an effective antioxidant in different in vitro assays including: reducing power, $DPPH^{\bullet}$, $ABTS^{\bullet+}$, $O_2^{\bullet-}$ and $DMPD^{\bullet+}$ radical scavenging, hydrogen peroxide scavenging and metal chelating activities when compared to standard antioxidant and concluded that it was the H-atom donation from the phenolic group which was responsible for the "superb antioxidant" properties of curcumin (15).

Nonsurgical periodontal therapy (NSPT) is the foundation of periodontal therapy and the first step to the control of periodontal infections. It is an combination of "plaque removal, plaque control, supragingival and subgingival scaling root planing (SRP), and use of any adjunctive (16). Scaling and Root Planing (SRP) is the gold standard treatment for most patients with periodontitis (17)

The goal of this study was to know the anti oxidant effects of curcumin lozenges in patients with periodontitis, patients where divided into two groups and plaque removal, plaque control and then SRP was performed in both the groups. Curcumin lozenges was given as an adjunct for Group II whereas Group I no adjunct was given.

The results obtained from this study correlated with other major studies done with curcumin before, like In a study done by Chapple et al, the concentrations of both types of glutathione peroxidase was reduced in GCF chronic periodontitis patients (18).

Which coincides with the result we obtained in our study where glutathione peroxidase was significantly less on day 1 in both Group I AND II when compared to compared to group II DAY 50, where the glutathione peroxidase was

significantly more. SOD levels were also seen higher in GROUP II on day 50 compared to day 1 suggesting CURCUMIN LOZENGES as an potent and easy to consume adjunct to SRP.

**Conclusions**

Curcumin is a naturally gifted molecule that is humongous in its antioxidant capacity so when combined as an adjunct to SRP it has provided us with commendable results, also curcumin in the form of lozenges are way easier to consume when compared to other traditional ways, thus these Curcumin lozenges can be recommended to Periodontitis patients as an adjunct along with SRP in the future.

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