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Effect of Turmeric on Serum Malondialdehyde in Oral Submucous Fibrosis

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ABSTRACT

Introduction: Betel nut consumption with or without tobacco and betel nut infested with *Aspergillus* flavours, generates free radicals and reactive oxygen species, which in turn induces a high rate of lipid peroxidation. Serum Malondialdehyde (MDA) is a highly recognized marker of lipid peroxidation. **Objective:** The present study was conducted to evaluate the effect of turmeric on increased lipid peroxidation by using serum MDA level & as a surrogate outcome on clinical signs & symptoms of oral submucous fibrosis (OSMF).

Material and Methods: Total of 150 subjects was divided into 4 groups. Group A: 30 subjects suffering from OSMF were treated with turmeric and counselled for stoppage of habit, Group B: 30 subjects suffering from OSMF were treated with turmeric and NOT counselled for the cessation of habit, Group C: 30 subjects suffering from OSMF did not keep on turmeric medication but counselled for stoppage of habit, Group D: 30 cases were betel-nut habitual without OSMF and Group E: 30 healthy control subjects.

Results and Observations: Statistically significant reduction of Serum MDA levels post-treatment in group A patients as compared to group B & group C ($p < 0.05$). Mean difference was observed as 9.00 in group A, 3.81 in group B, 2.62 in group C.

Conclusion: Increased serum Malondialdehyde (MDA) in OSMF would serve as a valuable surrogate marker in early diagnosis, treatment, and prognosis. The antioxidant properties of turmeric reduce the oxidative stress even with the effects of areca alkaloids and tobacco. Serum MDA level was decreased significantly in subjects taking turmeric medication for 4 weeks.

Key Words: OSMF, Betel-nut, Lipid peroxidation, Malondialdehyde

INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a slowly progressive chronic condition of mainly involving non-keratinized mucosa of the mouth and characterized by fibrosis from epithelium to basement membrane; causing the inability to open mouth, blow/whistle, and speech & eat.¹ In Indian population OSMF is about 0.5%.² Betel nut habit is the principal culprit in pathogenesis & development of OSMF. Ingestion of chillies, nutritional deficiency, autoimmunity and genetic susceptibility, immunologic process and nutritional deficiencies are considered as cofactors.³

Interaction of free radicals & reactive oxygen species (ROS) with lipid, DNA & proteins is responsible for the degradation of proteins & promote DNA strand breakage & harms genomic structure. Lipid peroxidation is causing uninterrupted generation of free radicals responsible for tissue injury. Thus, generated damaging aldehydes, malondialdehyde (MDA) are the quality marker for lipid peroxidation.^{4,5} Oxidative stress is produced by ROS & continuous transportation of oxygen to various parts of the body/organ and is safely detoxified by natural living antioxidants.⁶

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Turmeric is a polyphenol derived from roots of *Curcuma longa* plant. Turmeric is widely used in Indian system of Medicine Ayurveda. Curcumin (diferuloylmethane) main ingredient of turmeric is a carotenoid pigment, has anti-oxidant, analgesic, anti-inflammatory, anti-proliferative, anti-angiogenic, apoptosis-inducing, hepatoprotective & antiseptic activities.⁷⁻¹⁰ Hence, we conducted this study for evaluating the effect of the whole turmeric on lipid peroxidation in patients with OSMF.

MATERIAL AND METHODS

This study was carried out in the Oral Medicine department, SPDC, DMIMS (DU) Wardha after obtaining ethical approval from the Institutional Ethics Committee. Detailed clinical examination of all patients was carried out & recorded in structured proforma, after obtaining informed written consent. All patients were included by purposive sampling. A total of 150 subjects were recruited as follow-

Group A-30 suffering from OSMF on turmeric as well as counselled regarding stoppage of habit.

Group B-30 subjects suffering from OSMF on turmeric without counselling about the stoppage of habit. For these patients, counselling session was conducted after the study schedule.

Group C-30 subjects suffering from OSMF counselled for stoppage of habit but without turmeric medication. For these patients treatment protocol was started after study schedule.

Group D-Habitual controls, (30-Subjects Betel nut Habitual without OSMF) and

Group E-Healthy controls, (30- Subjects Without any detrimental Habit) were selected from persons accompanying with OSMF cases.

Inclusion Criteria was patient's above the age of 18 years clinically diagnosed as OSMF according to clinical & functional staging.¹¹ Raw turmeric was purchased & turmeric powder was prepared using pulverization procedure. Curcumin level was estimated by HPLC & 500 mg powder containing 5.9 mg of curcumin. 500 mg turmeric capsules were prescribed twice daily for four weeks and evaluated at end of 4th week for clinical signs and symptoms & serum malondialdehyde (MDA) level. Venous blood samples were collected pre-treatment & post-treatment for MDA estimation. VAS scale was used encoding 10 scores according to severity of symptoms regarding patient's perception of Burning Sensation to spicy foods, Tightness of fibrous bands, and Roughness of mucosa, Ulceration, Tongue movement and inter-incisal distance both pre & post treatment. Serum MDA was assayed by the modified Satoh Kei method (1978).¹² MDA concentration was calculated as $\eta\text{mol/ml}$ pre & post treat-

ment in groups A, B, C and in group D & E only single sample was estimated for MDA. Statistical Analysis was done by using descriptive and inferential statistics.

RESULTS

The mean age of OSMF patients in group A was found to be 32.26 ± 12.47 years, in group B 31.16 ± 10.86 years and group C 29.8 ± 7.25 years. The mean age in Group D was found to be 36.1 ± 15.64 years and in Group E it was 29.8 ± 8.94 years. The mean age of all OSMF patients (Group A, B & C) was 31.07 ± 10.36 years. Most of the patients of OSMF were young adults in the age group of 18-45yrs. 95% of patients were male and male to female ratio was 10:1. A maximum number of patients 83 (92.22%) had a habit of Kharrah & betel nut chewing. Mean duration of habit in OSMF study subject (Group A, B & C) was 7.66 ± 6.66 years while in habitual control (Group-D) it was 5 ± 2.78 years (Table 1 and 2).

Pre-treatment Serum MDA level in OSMF patient, group A, B & C was elevated [group A- $20.79 \pm 7.15 \eta\text{mol/ml}$, group B- $21.04 \pm 5.84 \eta\text{mol/ml}$, & group C- $22.72 \pm 6.33 \eta\text{mol/ml}$] as compared to habitual control- Group D & healthy control-Group E [$9.36 \pm 1.05 \eta\text{mol/ml}$ & $5.80 \pm 1.77 \eta\text{mol/ml}$ respectively] and showed statistical significance ($p=0.000$) (Table-3).

Significant decrease in post-treatment Serum Malondialdehyde levels was found in group-A patients (mean difference-9.00) as compared to groups-B (mean difference-3.81) & groups-C (mean difference-2.62) (Table 4). There was a significant increase in inter-incisal mouth opening, reduction in burning sensation, reduction in the tautness of fibrous bands, and reduction in ulcerations in Group- A in contrast to Group- B after giving whole turmeric capsules as a part of medication along with stoppage of habit ($p<0.05$) (Tables-5).

DISCUSSION

OSMF is a deliberating condition with considerable malignant potential. Arecoline is the principal alkaloid responsible for the pathogenesis of OSMF includes fibroblastic proliferation and increased collagen formation.¹³ Aflatoxin contaminated betel nuts along with alkaloids intensifies lipid peroxidation and decreasing enzymatic and non-enzymatic antioxidants.¹⁴ The free radical especially Hydroxyl radical is an extremely aggressive oxidant that can damage most of the biological molecule of the cell by lipid peroxidation, oxidative modification of proteins and DNA base alteration. MDA is a frequently used biomarker that provides overall information regarding lipid peroxidation.¹⁵ Evaluation of serum MDA level may be used as a potential surrogate marker for evaluating disease process in Oral submucous fibrosis.

In phase-I clinical trials, it is reported that curcumin 12 gm/day is well tolerated.¹⁶ It has been signified that curcumin has superior scavenging property as compared to beta carotene on superoxide radicals, free radicals and lipid peroxidation.¹⁷ Both turmeric oil and curcumin could work in an alliance of their anti-inflammatory and anti-cancer effects.^{18,19} Soma Gupta et al., observed the raised Plasma MDA levels in OSMF patients ($3.3 \pm 0.4 \mu\text{mol/ml}$) compared to healthy controls ($2.4 \pm 0.5 \mu\text{mol/ml}$); ($P < 0.001$). Decreased post-treatment mean MDA and increase in beta-carotene level were also observed in the same group of patients ($P < 0.001$).^{20,21} Increased mean serum malondialdehyde level in Oral Pre-cancer & Cancer $9.33 \pm 4.89 \mu\text{mol/ml}$ and $14.34 \pm 1.43 \mu\text{mol/ml}$ respectively as compared to control $5.107 \pm 2.32 \mu\text{mol/ml}$.²² In the present study, pretreatment serum MDA level was elevated in OSMF patients (group A, B & C) as compared to controls (Table 3 & 4). This suggests the role of lipid peroxidation i.e. oxidative stress & ROS in the pathogenesis of oral submucous fibrosis. Similarly, there was a significant reduction in serum MDA level post-treatment in OSMF groups (A, B, C) ($p < 0.000$), with more reduction, was observed in Group A in contrast to Group B (Table-4). This showed that stoppage of habit with turmeric medication had a significant effect on lipid peroxidation (MDA) & clinical signs & symptoms. In group B patients, turmeric medication showed its antioxidant & anti-inflammatory properties without cessation of the habit. This explains that betel nut alkaloid induced oxidative stress is relieved by the whole turmeric which is correlated with MDA level. On comparing habitual & healthy controls (groups D & E), increased MDA level in habitual controls indicates that lipid peroxidation is initiated by betel nut products with or without tobacco well before clinically evident disease process of OSMF. Kuttan Ramadasan et al., used ethanol extract of turmeric as a topical therapy in cancer of oral cavity and reported improvement in 64.80% of the patients.²³

Turmeric has been showing fibrinolytic action in iron-induced hepatotoxicity and improvement in liver functions AST, ALT & ALP to the normal level by inclusion of dietary turmeric, chilli pepper, cardamom, or clove in daily food of rat.²⁴ Manjunatha and Srinivasan demonstrated that dietary turmeric and capsaicin in chilli pepper notably repressed iron-induced Low-Density Lipoprotein (LDL), in vivo and copper-induced oxidation of Low-Density Lipoprotein, in vitro. The protecting effectivity of combination of turmeric and capsaicin on LDL oxidation was significantly higher than that of single components.²⁵ Balwant Rai et al., observed the significant symptomatic relief and reduction in the clinical size of oral Leukoplakia, treated with curcumin.²⁶

In the given study significant reduction of serum MDA levels was observed between pre & post-treatment with twice-daily 500 mg turmeric capsules at end of 4 weeks. Significant improvement in clinical signs & symptoms were observed in

group A as compared to B & C (Table-5). Sharma C et al. demonstrated that curcumin remarkably reduced nicotine acquired nitrosamine ketone cyclooxygenase-2 in oral pre-malignant as well as malignant cells in vitro.²⁷ Jayashree et al. observed that turmeric extract and turmeric oil (TO) in doses of 0.6 ml and 1.0 ml for 3 months of continuous daily intake had preventive properties against chemically generated carcinomas in lab animals.²⁸ Deepa Das et al., treated OSMF patients with curcumin & Turmeric oil for one month and reported significant improvement in clinical signs and symptoms.²⁹ Mrunal Meshram et al. used turmeric ointment twice daily for 03 months in oral submucous fibrosis patients and observed significant improvement in clinical symptoms.^{30,31} Bhide & Jakhi put out relief from clinical symptoms and refinement in the opening of the jaw with turmeric extract and its oil in total of 30 cases of oral submucous fibrosis.³² Similarly in present study statistically significant increase in inter-incisal opening & reduction in burning sensation was observed in group A & B but more significant in group A patients who were on turmeric medication with stoppage of habit (Table-5). Deng YT et al. observed dose-dependent complete inhibition of arecoline induced connective tissue growth factor (CTGF) in their in vivo study on human buccal mucosal fibroblasts treated with curcumin.³³ This suggests its fibrinolytic activity. Similarly, in the present study, a significant reduction in the toughness of fibrous bands i.e. clinical improvement in the elasticity of oral mucosa was observed in group-A patients as compared to groups B & C & was directly proportional to the level of serum MDA (Table-4 & 5). Curcumin also inhibits cell proliferation in fibroblast and myofibroblast; disturbs cell cycle, impel apoptosis as well as reduces decreases the generation type I and III collagen in myofibroblast.³⁴⁻³⁶ Prior types of research have proved that turmeric can interfere at varied phases of the cell cycle through suppression of DNA synthesis, downregulation of cyclin D1, provocation of p53 and cyclin-dependent kinase inhibitors, as well as retardation of NF- κ B.³⁷⁻³⁹

Prakasunand C et al., observed in 54 cases of peptic ulcer who were given 2 capsules of turmeric (300 mg each) 5 times daily for 4 weeks & reached a healing rate of 48%.⁴⁰ Similarly in the present study, we observed reduction in ulceration of oral mucosa in 40% of OSMF patients (groups A & B). Significant reduction is observed in group A after giving turmeric capsules & with stoppage of habit ($p < 0.05$) (Table-5). The curing effects of turmeric has been illustrated in Ayurveda and further traditional branches and confirmed by several experimental studies that it can arrest of carcinogenesis and also capable for reversal of the OSMF.^{16,41,42}

Reduced bioavailability of oral curcumin is related with its rapid metabolism due to its less effective conjugated form⁴³ but Robert CG Martin et al. suggested that of curcumin in precursor form can yield resistance to the fast metabolism which takes place in the upper gastrointestinal tract and

comes up with superior organ penetrance than that of with turmeric oil & curcuminoids which through the enzymatic process in the gastrointestinal tract got absorbed more efficiently. Therefore, in the present study whole turmeric could be more beneficial as it contains curcumin,

Table 1: Demographic Characteristics of Study & Control Groups

Characteristics	GP-A (n=30)	GP-B (n=30)	GP-C (n=30)	GP-D (n=30)	GP-E (n=30)
Age in Years					
Mean	32.26	31.16	29.82	36.15	29.80
SD	12.47	10.86	7.25	15.64	8.94
Range	18-60	19-62	18-45	16-65	19-55
Gender (%)					
Male	93.33	96.66	90	90	70
Female	6.66	3.33	10	10	30
M:F Ratio			10:1		

Table 2: Habit Characteristics of study & Habitual Control

Characteristics	GP-A (n=30)	GP-B (n=30)	GP-C (n=30)	GP-D (n=30)
Type of Habit				
Kharrha & Betel Nut	20	19	23	21
Kharrha & Gutkha	3	2	2	6
Betel Nut	7	9	5	3
Duration of Habit (years)				
Mean	9.96	6.93	6.11	5
SD	12.36	4.63	3	2.78
Range	May-30	May-20	May-15	05-Oct

Table 3: Comparison of Mean Serum Malondialdehyde levels in all groups

Groups	N	Mean Serum MDA (Pretreatment)	SEM±SD	Std. Deviation
Group-A	30	20.7997	1.30582	7.15227
Group-B	30	21.047	1.06777	5.8484
Group-C	30	22.72	1.15575	6.3303
Group-D	30	9.365	0.33391	1.05592
Group-E	30	5.805	0.56036	1.77202

Table 4: Comparison of Mean Serum Malondialdehyde levels at pre and post-treatment in study groups (N= 30)

Groups		Mean	Std. Deviation	Std. Error Mean	Mean Difference	t-value	p-value
Group A	Pre t/t	20.79	7.15227	1.3058	9.00867	13.193	0
	Post t/t	11.79	4.76103	0.8692			
Group B	Pre t/t	21.04	5.8484	1.0677	3.815	13.312	0.000 S,p<0.05
	Post t/t	17.23	5.35388	0.9774			
Group C	Pre t/t	22.72	6.3303	1.1557	2.62967	15.734	0.000 S,p<0.05
	Post t/t	20.09	6.07482	1.1091			

Table 5: Clinical Pre and post Treatment Characteristics of Study Group

Characteristics	Group A n=30		Group B n=30		Group C n=30	
	Pre T/t	Post T/t	Pre T/t	Post T/t	Pre T/t	Post T/t
Inter incisal mouth opening						
Mean	25.33	27.43	23.4	24.33	25.3	26.9
SD	7.01	6.8	7.48	7.5	8.52	8.59
Mean difference		2.1		0.93333		1.6
P value		0		0		0
Burning mucosa						
Mean	3.6	1.5333	3.3	2.4667	3.3	1.8
SD	1.13259	1.22428	0.83666	0.9732	0.70221	0.80516
Mean difference		2.06667		0.83333		1.5
P value		0		0		0
Tautness of fibrous bands						
Mean	2.7	1.46	2.43	1.83	2.56	1.76
SD	0.70221	0.57135	0.72793	0.69893	0.62601	0.85836
Mean difference		1.23333		0.6		0.8
P value		0		0		0
Tongue movement						
Mean	(20)* 3.0667	2.4667	(17)*2.7333	2.4333	(21)* 2.100	1.8333
SD	1.201	1.166	1.142	1.006	1.373	1.205
Mean difference		0.6		0.3		0.26667
P value		0		0.001		0.003
Oral ulceration						
Mean	(12)*1.36	0.16	(9)*0.86	0.46	(15)*0.56	0.13
SD	0.96431	0.37905	0.68145	0.57135	0.67891	0.34575
Mean difference		1.2		0.4		0.43333
P value		0		0		0

()*=number of cases

CONCLUSION

Serum MDA measures were observed to be elevated in oral submucous fibrosis when equating to habitual & healthy control. Individuals, on turmeric medication for 4 weeks showed significantly reduced MDA level. Thus, the level of lipid peroxidation i.e. oxidative stress is decreased after oral administration of turmeric. Similarly, the oral submucous fibrosis patients are relieved from clinical signs & symptoms particularly improved inter-incisal distance & toughness of fibrous bands thus turmeric may act as an anti-fibrotic.

Turmeric has excellent antioxidant, anti-proliferative, anti-inflammatory, antiviral, antibacterial, antifungal, analgesic,

anti-allergic and antiseptic effects which signify its potential use in treatment oral Potentially Malignant Disorders (PMDs) like OSMF. Thus, this choice of therapy accompanied with stoppage of habit is beneficial, affordable and noninvasive to patients with OSMF to control the malignant transformation.

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