Sesamol: An Efficient Antioxidant with Potential Therapeutic Benefits

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Abstract: Sesamol has been shown earlier to exhibit antimutagenic (reactive oxygen mediated) and antiageing activity in our lab and it has also been found to exert chemopreventive effect. Here we report the *in vitro* antioxidant activity of sesamol. As most of the antioxidants act due to their property to auto-oxidise and the pro- or antioxidant activity would depend on the concentration of the agent used and the free radical source, at least 6 dilutions in concentration range of 5-1000 nmoles of sesamol were selected for each test system. Further the antioxidant activity was compared with a water soluble antioxidant (ascorbic acid). Eventhough some preliminary studies on the antioxidant activity of sesamol have been reported in DPPH assay & inhibition of lipid peroxidation, it is not complete. We, here in report comprehensively (both in terms of the no. of doses and also a variety of test systems being employed) on the antioxidant activity of sesamol. Furthermore, since all the data has been generated by the same workers and under same laboratory conditions, hence is scientifically significant. Also the process of dose selection as discussed earlier is more scientific; and the data treatment, i.e. calculation of IC_{50} values and comparisons with ascorbic acid has been statistically validated.

In conclusion, sesamol was found to be an efficient scavenger of the entire range of ROS in several test systems pointing towards the potential of sesamol to be developed as a possible therapeutic.

Key Words: Sesamol, total antioxidant capacity, DPPH assay, superoxide anion scavenging, hydrogen peroxide scavenging, hydroxyl radical scavenging, nitric oxide scavenging, lipid peroxidation.

INTRODUCTION

Free radicals have been implicated as causative agents in various ailments such as liver cirrhosis, cardio vascular disorders, diabetes, cancer & mutagenesis, and several neurodegenerative disorders and the aging process. Antioxidants that scavenge free radicals have found great potential in ameliorating these disease processes. Hence in the past few years natural antioxidants have generated considerable interest in possible prevention of disease.

Sesame, an important oilseed from *Sesamum indicum*, is one of the oldest known to man, and is considered to possess not only nutritional value, but also some medicinal value. It was employed in ancient Chinese medicine as an energy booster and to prevent aging [1]. Sesame (along with coconut) is one of the two oldest oilseeds known to man. The core of the multifaceted aspect of sesamum species is its antioxidant status. This is attributed mainly to the presence of a variety of polyphenolic substances including sesamol.

Sesamol, 5-hydroxy-1,3-benzodioxole or 3,4-methylenedioxyphenol has been found to be a good antioxidant. It has a benzodioxole group, which is known to scavange hydroxyl radical to produce 1,2-dihydroxybenzene [2]; later is also an antioxidant. Sesamol is a very effective inhibitor of lipid peroxidation of rat liver microsomes [3]. It has also been shown to exhibit antimutagenic activity against oxygen species mediated mutagenicity in *Salmonella typhimurium* TA100 and TA102 strains; this activity was demonstrated to be due to its antioxidant activity by us [4]. It is also reported to show antioxidant activity in UV, Fe (II), Fe (III) and cupric oxide induced lipid peroxidation [5, 6]. Sesamol has also been found to scavenge DPPH radicals [7, 8], imidazoquinoxaline type radicals; a recent report indicates superoxide anion, hydroxyl radical & singlet oxygen scavenging [9, 10]. It has also been reported to inhibit hydroxyl radical induced deoxyribose degradation and DNA cleavage [6, 11]. Sesamol at very high doses (TD_{50} 16.2 & 41.3 g (300 mmoles) / day) administered for a period of 2 years is reported to induce stomach cancer [12-14] especially the forestomach in rodents [14]. Considering the high dose, long duration and the fact that humans do not have forestomach, these reports are insignificant. Furthermore, sesamol, butylated hydroxyanisole and caffeic acid are referred to as non-genotoxic carcinogens and the hyperplasia and papilloma induced by these agents readily regress after cessation of administration [15-18].

The antiageing property of sesamol was also tested in our laboratory and encouraging results were obtained [19]. Sesamol has also been found to exert chemopreventive effect (in the mouse skin two-stage carcinogenesis) and antimutagenic effects [10, 20, 21].

EXPERIMENTAL

Chemicals and Solvents

The chemicals used were of the highest available purity grade from commercial sources. Sesamol and ascorbic acid were obtained from Sigma Aldrich, Mo, USA and S.D fine chemicals Pvt. Ltd, Boisar, India respectively and were above 99% purity.

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Methods

In vitro antioxidant activity of sesamol in various test systems was carried out as per the recommended procedures cited in literature [3, 22-29] and our own review [30].

RESULTS AND DISCUSSION

Knowledge of the antioxidant activity of an agent and its activities with different oxidants is fundamental to understanding and predicting its capacity to protect biological tissues susceptible to oxidative stress. However, the complexity of cellular balance between oxidant challenge and antioxidant response often precludes generalization regarding the potential of ROS-mediated impact, based on the response of antioxidants to a single oxidant. Because the antioxidant capacity of chemicals or tissues varies with the kind of oxidants that attack them, the main aim of the present study was to establish the relative antioxidant potential of sesamol in a battery of test systems, ranging from DPPH assay (1, 1-Diphenyl picryl hydrazyl being a stable free radical) to hydroxyl radical scavenging. Latter is the most reactive of the oxygen radicals, with a very short half life and can combine with almost all molecules of the living cells. This is the first report on the antioxidant activity of sesamol in the entire battery of *in vitro* tests.

Most of the antioxidants act due to their property to autooxidize. In this process, there are chances of the formation of secondary free radicals which may be responsible for the pro-oxidant activity of these agents. The pro-oxidant activity would depend on the concentration of the agent used & the free radical source. Based on this, we tested sesamol initially in a wide concentration range (1 nmole-5 millimoles) & then the lowest dose range (1 nmole-1 µmole), in which a concentration dependent antioxidant activity was observed, is reported here in. At least 6 dilutions in concentration range of 5-1000 nmoles of sesamol were selected in each test system. All the results are expressed as IC_{50} values (Table **1**) obtained from the percent inhibition curve, which was plotted by taking concentration on X-axis & percent scavenging on Y-axis. IC_{50} value of sesamol (the amount of drug required to scavenge 50% of free radicals) was obtained from the above mentioned linear plots (r value > 0.92). The data was statistically analysed by one-way ANOVA followed by tukey's test for multiple pair wise comparison in all the test systems.

This study is an effort to make reliable comparisons of antioxidant activity of sesamol with ascorbic acid, and to present a comprehensive data on its activity in a battery of *in vitro* & *ex vivo* test systems, using a range of doses. Ascorbic acid was taken as a control instead of α-tocopherol since the latter is water insoluble antioxidant i.e., lipophilic while sesamol is highly water soluble. Considering this, we used ascorbic acid, a water soluble antioxidant. The results are also expressed in terms of ascorbic acid equivalents (Tables **1** & **2**). Ascorbic acid equivalent is the concentration in µmoles of ascorbic acid required to produce a same effect as that produced by 1 µmole of a test agent.

Ex vivo antioxidant activity of sesamol is also reported. *Ex vivo* model used here include the evaluation of inhibition of lipid peroxidation in brain and liver homogenates, induced by Fe^{+3}. Considering that lipids are the main components of cell membrane, peroxidation of lipids can contribute to cancer & aging. Lipid peroxidation has been reported to mediate 8-OH deoxy guanosine (8-OH dG) formation *in vitro* [31]. Latter is an important marker of oxidative damage and may also play a role in carcinogenesis. Kang *et al*. have reported that the amount of 8-OHdG in the urine of rats fed on 1 % sesamolin was significantly lower than that in the rats fed on a control diet (Sesamolin is one of the lignans found in sesame oil) [32]. Further, since tissue homogenates are being used and protection against lipid peroxidation would require the drug molecule to enter the cell, permeability of the former would also have a role to play in its efficacy.

Sesamol was found to be an efficient scavenger of the entire range of ROS against which its activity was evaluated. Further, in most of the test systems it was found to be more active than ascorbic acid (Tables **1** & **2**). The total antioxidant capacity of sesamol, determined on the basis of the phosphomolybdenum complex formed (indicative of antioxidant capacity; measured at 695 nm), was significantly higher than ascorbic acid. The plot of sesamol lies above that of ascorbic acid indicating that sesamol is a better antioxidant (Fig. (**1**)). Slope values (amount of phosphomolybdenum complex formed/µmole) of the plot(s) indicate that sesamol is 1.8 times more active than ascorbic acid. The latter may be taken as an ascorbic acid equivalent of sesamol in this test system. Similarly, sesamol showed a significantly better scavenging of DPPH radical (1.5 times), superoxide anion (6 times) & nitric oxide (2.5 times). While the hydroxyl radical and hydrogen peroxide scavenging capacity of sesamol was equivalent to ascorbic acid. The IC_{50} value of sesamol in the DPPH assay reported herein by us to be 46.03 nmoles compares well with that reported by Kapadia *et al*. [20] as 5.95 µg/ml which comes to 43.11 ± 5.41 nmoles. The IC_{50} value of ascorbic acid reported by these workers (27.16 ± 0.98 nmoles; reported as 4.78 ± 0.49 µg/ml) is however considerably different from the value reported by us i.e. 51.26 ± 0.98 nmoles. It may however be noted that the test systems used by these workers is different (we used 2 ml solution of a 100µM DPPH while Kapadia *et al*. have used 1.5ml of a 50µM solution) [20]. The number of doses tested and the dose range used in the study is also not mentioned by these workers. The free radical against DPPH scavenging capacity of sesame antioxidants in kinetic model indicated sesamol to be the most active [7]. It may be noted here that the antioxidant activity is observed at very low concentrations (IC_{50} value ranges from 25-375 nmoles) while the tumorogenic reports [14] on sesamol indicate the dose to range from 10-30 mmoles (41.3 g/kg body weight for 24 months) which is almost 10^6-10^8 times of that required for the antioxidant effect. Most of the antioxidants are expected to show a pro-oxidant effect at high doses, which may express itself in the form of carcinogenesis.

It may be observed from the results in Table **2** that sesamol is effective in inhibiting the lipid peroxidation induced in rat brains by Fe^{3+}. Results are expressed in terms of percentage inhibition of TBARS formed. Sesamol being a small molecule with a Log $P_{\text{octanol/water}}$ of 1.29 (favoring towards octanol; indicating lipophilicity) probably has a better permeability such that it showed a considerably higher activ-

Table 1. Percentage Inhibition with Sesamol and Ascorbic Acid in Various Test Systems

Conc. (nmoles)	PERCENTAGE INHIBITION ± SD					
Sesamol	**DPPH Assay**	**$^{\cdot}O_2$ Scavenging**	**H_2O_2 Scavenging**	**$OH^{\cdot}$ Scavenging**	**$NO^{\cdot}$ Scavenging**	**Lipid Peroxidation (Rat Liver)**
1000	-	-	-	-	60.50 ± 3.20	-
500	91.46 ± 1.02	83.30 ± 1.15	-	61.89 ± 2.94	54.39 ± 2.90	57.05 ± 0.43
250	89.51 ± 0.48	68.80 ± 2.06	67.75 ± 0.94	52.11 ± 2.60	50.16 ± 2.14	45.76 ± 5.90
125	87.29 ± 0.72	63.21 ± 3.54	48.58 ± 0.94	46.30 ± 3.61	46.87 ± 2.82	29.19 ± 0.43
100	-	-	-	-	-	-
50	59.78 ± 2.67	52.51 ± 3.51	35.65 ± 0.24	36.63 ± 5.11	42.75 ± 3.30	19.92 ± 5.01
25	38.49 ± 2.41	-	28.24 ± 0.33	25.43 ± 3.19		9.73 ± 2.97
10	-	34.67 ± 2.99	-	-	-	-
5	27.98 ± 0.21	-	23.82 ± 0.80	-	-	-
IC_{50}	25.47	18.87	142.46*	184.03*	130.40	378.33
Ascorbic acid						
1000	-	-	-	-	59.67 ± 1.58	-
500	95.89 ± 0.71	-	-	57.23 ± 2.97	40.99 ± 2.23	70.58 ± 0.77
250	86.40 ± 0.80	-	66.34 ± 0.57	53.98 ± 3.48	38.48 ± 3.71	63.41 ± 0.37
125	81.97 ± 0.95	42.76 ± 0.82	44.62 ± 0.58	46.91 ± 2.76	35.08 ± 2.65	52.37 ± 2.32
100	-	-	-	-	-	-
50	50.42 ± 0.43	34.70 ± 1.95	36.13 ± 0.65	39.40 ± 3.26	32.91 ± 3.56	39.58 ± 1.70
25	30.37± 0.17	27.29 ± 1.91	-	33.11 ± 3.07	-	29.84 ± 0.87
10	-	18.44 ± 2.58	29.78 ± 1.74		-	-
5	-	-	29.11 ± 2.14		-	-
IC_{50}	37.60	103.40	146.56 *	189.38*	326.41	103.52
Ascorbic acid equivalents	1.48	5.48	1.08	1.03	2.5	0.29

* no statistically significant difference between the sesamol and ascorbic acid group.

ity (462 times that of ascorbic acid expressed as the ascorbic acid equivalent; Table **2**). It may thus be concluded here that sesamol can be used to alleviate pathologies of brain associated with oxidative stress. The IC_{50} of sesamol, as obtained from log concentration *vs* % inhibition curve was 0.07 mmoles. Similar, effects have been reported earlier [6].

However, in inhibiting lipid peroxidation in rat liver (IC_{50} = 0.378 µmoles) it may be noted that ascorbic acid showed a 3 times higher activity. A better activity shown by vitamin C (in comparison to sesamol) for inhibiting the lipid peroxidation levels could be due to the natural presence of ascorbic acid in biomembranes. Ascorbic acid is regarded as the major aqueous phase endogenous antioxidant. This may help in the better uptake of ascorbic acid from the surrounding aqueous medium; ascorbic acid has a high solubility also. Solubility of ascorbic acid is reported to be 330 mg/ml; and the solubility of sesamol, as found by us, is 38.8 ± 1.2 mg/ml.

Ex vivo inhibition of lipid peroxidation in liver microsomal fractions or hepatocytes by sesamol, has also been reported by other workers. Kang *et al*. have reported a 12% inhibition of LPO levels by 10nmoles/ml of sesamol. Further Kang *et al*. have also indicated a protective role of sesamolin (it hydrolysis to give sesamol) on lipid peroxidation indicated by lower amounts of 8-OH dG in the urine of rats fed on 1 % sesamolin [32]. Similarly a 97.04% inhibition of LPO by 50µM concentration of sesamol (single dose tested), induced by ferric nitrilotriacetate & ascorbic acid has been

Table 2. Inhibition of Lipid Peroxidation Induced by $FeCl_3$ in Rat Brain Homogenate by Varying Concentrations of Sesamol and Ascorbic Acid

Concentration of Sesamol (mmoles)	% Inhibition ± S.D.	Concentration of Ascorbic Acid (mmoles)	% Inhibition ± S.D.
Inducer only	0.00±0.00	Inducer only	0.00 ± 0.00
0.2	44.32±4.05	1	12.85 ± 2.96
0.4	72.49±4.91	5	15.71 ± 1.88
1	95.29±0.96	10	38.57 ± 3.3
2	97.25±1.12	50	46.19 ± 2.14
		100	73.33 ± 2.9
IC_{50} (mmole)	0.07	32.35	
Ascorbic acid equivalent		462.14	

reported [33]. In our studies, sesamol showed 57.04% inhibition of LPO at 500nmoles (0.5 μmoles). However, these workers have used isolated rat hepatocytes or the microsomal fraction of the rat liver homogenates rather than the complete homogenates.

Considering the strong antioxidant potential of sesamol *in vitro*; incorporation of this molecule into a novel delivery system, which can improve its permeability and help in its sustained release across the membranes and at the biological site can be derived as a corollary of the present research work.

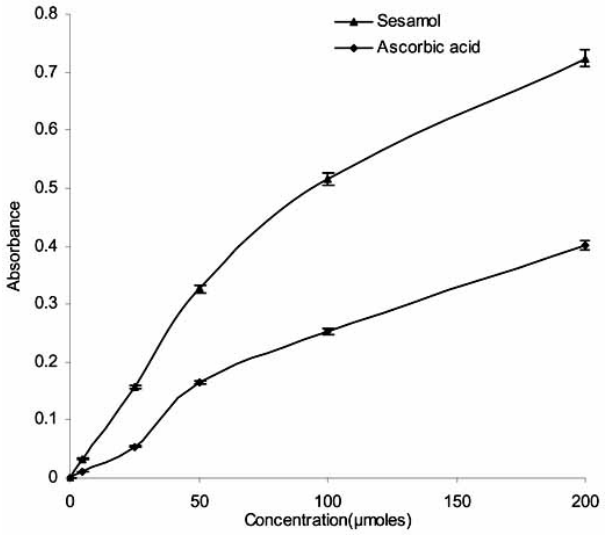

Fig. (1). Concentration of sesamol and ascorbic acid *vs*. phosphomolybdenum complex (n=5), expressing the total antioxidant capacity.

CONCLUSIONS

If we are determining the different free radical scavenging activity of a particular compound, we explore its possible use in a multitude of disease states caused by those free radicals. However, *in vitro* scavenging is only a preliminary test for selecting potent antioxidants. The promising antioxidant activity shown by sesamol, needs to be followed by an *in vivo* evaluation of sesamol for its potential usefulness in the control of diseases whose pathophysiology involves free radicals. Our earlier studies indicate sesamol to possess antimutagenic activity in the Ames test [4] and antiphotoaging effects, *in vivo*, in mice [19]. Evaluation of its physicochemical parameters (solubility is 38.8 ± 1.2 mg/ml; log $P_{octanol/water}$ 1.29 ± 0.01, mol. wt. 138.34 g), indicate it to be an interesting and unique phenolic compound (due to its solubility in aqueous as well as oil phase) which has a potential for development as a therapeutic agent, especially considering its high superoxide and $NO^{\cdot}$ scavenging which was even significantly better than catechin and epicatechin (IC_{50} for sesamol, catechin, epicatechin and ascorbic acid is 130.4, 188.3, 212.8 and 326.4 nmoles respectively).

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