

Sesamin and Sesamol: Nature's Therapeutic Lignans

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Abstract: Sesame oil is commonly used as antioxidant. Sesamin (SA) and sesamol (SO) are major lignans (a non-fat constituent) in sesame seed oil, inhibit Δ 5-desaturase activity and cause accumulation of dihomo- γ -linolenic acid (DGLA), a precursor of 1-series prostaglandins, and the decreasing production of pro-inflammatory 2-series prostaglandins and 4-series leukotrienes. Diets supplemented with SA and/or SO, lower serum levels of interleukin (IL)-1, IL-6 but elevate IL-10 in mice after lipopolysaccharide (LPS) exposure. Mice fed with sesame seed oil have a 65% survival rate after cecal ligation and puncture as compared with the 20% survival in the controls. SA and SO inhibit the IL-6, tumor necrosis factor (TNF)- α and nitric oxide (NO) productions from microglia under LPS stimulation. The protective effects of SA/SO to stroke-prone spontaneously hypertensive rats and hepatic ischemia-reperfusion injury have been attributed to their antioxidant and anti-inflammatory activities. The antioxidant activities of SA/SO are identified in their methylenedioxyphenyl moieties that can be changed into dihydroxyphenyl (catechol) moieties. Since reactive oxygen species (ROS) are mediators of a variety of pathological processes, including inflammation and ischemic/hypoxic injury, the ROS scavenging moiety may contribute as an important component to prevent cells from the free radical injury. Hypoxia or H₂O₂-induced cell injury are related with activated MAPKs and caspase-3 activities. Evidence suggests that the protective effects of SA and SO on hypoxic neuronal cells are related to suppression of ROS generation and mitogen-activated protein kinases (MAPKs). In addition, SA/SO significantly reduce LPS-activated p38 MAPK. Specific inhibitors of MAPKs dose-dependently inhibit NO and cytokine productions in LPS-stimulated microglia. Therefore, the inhibition of NO and cytokine productions may partly be due to the reduction of LPS-induced p38 MAPK signal pathway by SA and SO.

Keywords: Sesamin, sesamol, hypoxia, lipopolysaccharide, reactive oxygen species, mitogen-activated protein kinases, antioxidant, anti-inflammation.

INTRODUCTION

Sesame lignans such as sesamin, episesamin, and sesamol, and γ -tocopherol from *Sesamum indicum* seeds (Fig. 1) play important roles in plant defense, such as antifungal as well as potent antioxidants and insecticides [1-4]. Sesamin is the most abundant lignan in sesame seed [1,2,5] and found in various medicinal plants [6-11]. Sesamin enhances hepatic detoxification of chemicals [12], reduces the incidence of chemically induced tumors [13], and protects neuronal cells against oxidative stress [14,15]. Sesamin exhibits anti-hypertensive [16], anti-inflammatory [17-19] and anti-allergic effect [20].

Many health benefits of sesame may be attributed to its lignans, especially sesamin [2]. Yet, the physiological effect of sesamin has been studied only in recent years. Sesamin and episesamin (an epimer of sesamin) are incorporated into the liver after administration and then transported to the other tissues (lung, heart, kidney, and brain). They are lost from the body within 24 h after administration. Sesamin and episesamin has similar lymphatic absorption, but the amount of sesamin is significantly lower than that of episesamin in all tissues and serum [21]. The structure difference between sesamin and sesamol (see Fig. 1) is the oxygen insertion between the furfuran and piperonyl (methylenedioxyphenyl) groups [22]. Methylenedioxyphenyl

compounds are demethylated by cytochrome P450 catalyzed oxidation [23].

EFFECT ON LIPID METABOLISM

Sesamin specifically inhibits Δ 5 desaturase at low concentrations may be important for its anti-inflammatory effect. It does not inhibit Δ 6, Δ 9 and Δ 12 desaturases in a cell-free extract of the fungus or rat liver microsomes. Δ 5-desaturase is the enzyme for the conversion from dihomo- γ -linolenic acid (DGLA, 20:3, n-6) to arachidonic acid (AA, 20:4, n-6). Kinetic analysis showed that sesamin is a noncompetitive inhibitor (K_i for rat liver Δ 5 desaturase, 155 μ M). Sesamol, sesaminol and episesamin also inhibited only Δ 5 desaturases of the fungus and liver [24]. Sesamin (0.5% w/w) increases the liver weight and phospholipid contents in liver of rats under γ -linolenic acid-rich diet or γ -linolenic acid-rich diet for 4 weeks. It increases n-6 fatty acids (FA) and decreases n-3 FA even though the diet is rich in n-3 FA. Sesamin decreases of Δ 5-desaturation index of n-6 FA, the ratio of 20:4(n-6)/20:3(n-6) but it increases Δ 5-desaturation index of n-3 FA, the ratio of 20:5(n-3) to 18:3(n-3) in the liver of rats fed γ -linolenic acid-rich diet [17]. Sesamin and episesamin affect the n-6/n-3 ratio of polyunsaturated fatty acid (PUFA) in rat liver. For 4 wk, rats are fed two types of dietary oils (i) the control oil diet groups (CO): soybean oil/perilla oil = 5:1, and (ii) the AA-rich oil group (AO): AA ethyl esters/palm oil/perilla oil = 2:2:1, with or without 0.5% (w/w) of sesame lignans. AA content and n-6/n-3 ratio in the liver are significantly increased in the AO group, despite the dietary total of n-6 PUFA being the

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same in all groups, while sesamin dietary group (AOS) reduced AA content and n-6/n-3 ratio to a level similar to the CO and COS groups [25]. Therefore, anti-inflammatory effect of sesamin may due to the inhibition of $\Delta 5$ desaturase.

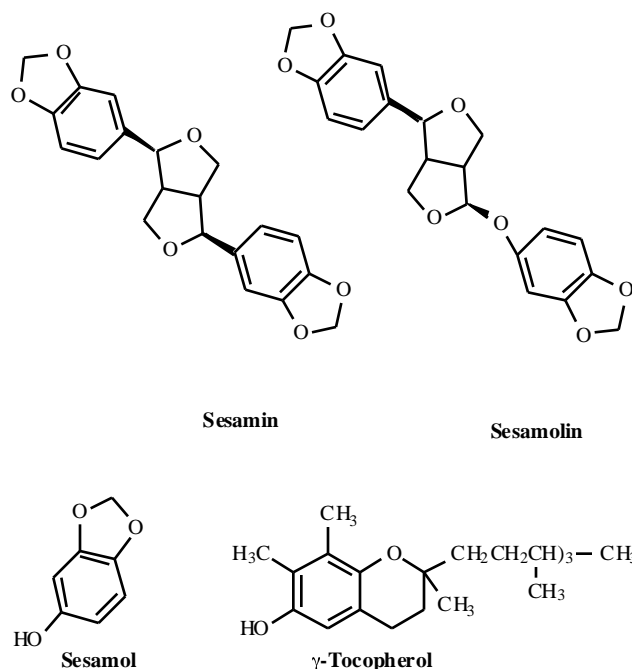


Fig. (1). Chemical structure of a few bioactive compounds of sesame.

FATTY ACID OXIDATION

Sesamin increases hepatic fatty acid β -oxidation and decreases the hepatic lipogenic activity. This may account for the serum lipid-lowering effect in human and rats (discussed in next section). In rats fed with experimental diets containing various amounts (0%, 0.1%, 0.2%, and 0.5%) of sesamin (a 1:1 mixture of sesamin and episesamin) for 15 days, sesamin dose-dependently increases both mitochondrial and peroxisomal palmitoyl-coenzyme A (CoA) oxidation rates [26]. Mitochondrial activity almost doubles in rats on the 0.5% sesamin diet. Peroxisomal activity increases more than 10-fold in rats fed a 0.5% sesamin diet in relation to rats on the sesamin-free diet. Sesamin greatly increased the hepatic activity of fatty acid oxidation enzymes (Table 1), including carnitine palmitoyltransferase, acyl-CoA dehydrogenase, acyl-CoA oxidase, 3-hydroxyacyl-CoA dehydrogenase, enoyl-CoA hydratase, and 3-ketoacyl-CoA thiolase. The activity of 2,4-dienoyl-CoA reductase and Δ^3 , Δ^2 -enoyl-CoA isomerase, enzymes involved in the auxiliary pathway for β -oxidation of unsaturated fatty acids is increased dose-dependently by sesamin. The gene expression of hepatic mitochondrial and peroxisomal fatty acid oxidation enzymes is also increased. Peroxisomal acyl-CoA oxidase and bifunctional enzyme gene expression are affected most by sesamin (15- and 50-fold increase by the 0.5% dietary level) [26]. The activities of carnitine acyltransferase and acyl-CoA dehydrogenase in liver mitochondria are enhanced by the intake of the high-fat diet (20% rapeseed oil: soybean oil, 7:3), and are further enhanced by the administration of sesamin. Peroxisomal

acyl-CoA oxidase activity is also enhanced by sesamin, while it is not affected by the dietary fat level [27]. Sesamin increases enzyme activities in all groups of rats given different fats. The extent of the increase depends on dietary fat type, and a diet containing sesamin and fish oil in combination appear to increase many of these parameters synergistically. In particular, the peroxisomal palmitoyl-CoA oxidation rate and acyl-CoA oxidase activity levels are much higher in rats fed sesamin and fish oil in combination than in animals fed sesamin and palm or safflower oil in combination [28]. In contrast, sesamin significantly decreases the hepatic lipogenic activity and mRNA of fatty acid synthase and pyruvate kinase (Table 1). However, this lignan also increases the activity and gene expression of malic enzyme, another lipogenic enzyme [26]. The decrease in lipogenic enzyme gene expression may also be due to the suppression of the gene expression of the sterol regulatory element binding protein-1 (SREBP-1). Sesamin dose-dependently decreases SREBP-1 mRNA level, and protein to less than one-fifth of that in the animals fed a sesamin-free diet [29]. The increase in hepatic fatty acid metabolism and decrease lipogenic enzymes may therefore account for the serum lipid-lowering effect of sesamin in the rat [26-30].

Table 1. Effects of Sesamin on Fatty Acid β -oxidation and Synthesis

Changes of enzyme activity	
β -oxidation	
Palmitoyl-coA	
mitochondrial and peroxisomal	
Carnitine palmitoyltransferase	
Acyl-CoA oxidase	
3-hydroxyacyl-CoA dehydrogenase	
3-ketoacyl-CoA thiolase	
2,4-dienoyl-CoA reductase	
Δ^3 , Δ^2 -enoyl-CoA isomerase	
Lipogenic activity	
Fatty acid synthase	
ATP-citrate lyase	
L-Pyruvate kinase	
Glucose-6-phosphate dehydrogenase	

[21,26,28]

Rats under diets containing 0.2% of sesamin or episesamin for 15 days have increased rates of the mitochondrial and peroxisomal palmitoyl-CoA oxidation. However, the magnitude of the increase is greater with episesamin than with sesamin. Sesamin caused 1.7- and 1.6-fold increases in mitochondrial and peroxisomal activity, respectively, while episesamin increased these values 2.3- and 5.1-fold. Episesamin increases the activity and gene expression of fatty acid oxidation enzymes greater than sesamin [30]. In general, sesamin increases hepatic activity and the mRNA levels of enzymes involved in fatty acid oxidation, while it strongly down-regulates those of enzymes

involved in lipogenesis in rats. In contrast, this lignan does not modify these variables in mice and hamsters [31].

REDUCTION OF CHOLESTEROL

The concentration of serum and liver cholesterol is significantly reduced by sesamin (Table 2). In rats supplemented with dietary level of 0.5% sesamin for 4 weeks, there is a decrease in lymphatic absorption of cholesterol accompanying an increase in fecal excretion of neutral, but not acidic, steroids, particularly when the cholesterol-enriched diet is given. Sesamin inhibits micellar solubility of cholesterol, but not bile acids, whereas it neither bound taurocholate nor affected the absorption of fatty acids. Only a marginal proportion (ca. 0.15%) of sesamin administered intragastrically is recovered in the lymph. There is a significant reduction in the activity of liver microsomal 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase after feeding sesamin, although the activity of hepatic cholesterol 7 α -hydroxylase, drug metabolizing enzymes, and alcohol dehydrogenase remains unchanged [32]. Effects of sesamin and episesamin on lipid metabolism, in particular cholesterol metabolism, were examined in normal cholesterolaemic and hypercholesterolaemic stroke-prone spontaneously hypertensive rats (SHRSP). In normocholesterolaemic SHRSP fed a regular diet, both sesamin and episesamin significantly increased the concentration of serum total cholesterol, which was due to an increase of high density lipoprotein (HDL) subfraction rich in apoE. In addition, both substances effectively decreased serum very low density lipoprotein (VLDL). In the liver, only episesamin significantly decreased the activity of microsomal acyl-CoA:cholesterol acyltransferase. In hypercholesterolaemic SHRSP fed a high-fat and high-cholesterol diet, only episesamin improved serum lipoprotein metabolism with an increase in apoA-I and a decrease in apoB [33]. In the liver, both sesamin and episesamin significantly suppressed cholesterol accumulation. Interestingly, only episesamin significantly increased the activity of microsomal cholesterol 7 α -

hydroxylase [21]. These results indicate that sesamin may be effective in preventing cholesterol accumulation in the liver [33,34 and Table 2]. Nutritional-induced hypercholesterolaemia in New Zealand rabbits causes increased susceptibility to experimental infections. Rabbits fed cholesterol (0.5 g%) for 8 weeks were injected intravenously with varying doses of *Escherichia coli* 0127: B8 lipopolysaccharide (LPS; 3-100 μ g/kg). The survival rate of hypercholesterolaemic rabbits (1/11) is lower than in normal rabbits (6/7) or rabbits fed with the sesame oil chow (4/4) at the higher LPS doses. No death occurs at lower doses. Neutralization of TNF experiments suggest that increased TNF secretion in hypercholesterolaemic rabbits raises the host's susceptibility to experimental endotoxaemia and possibly to Gram-negative infection [35]. In a clinical study with only 12 patients, sesamin significantly reduces total cholesterol (TC) level from 272 to 248 mg/dl, LDL-C from 187 to 156 mg/dl and apoB from 189 to 169 mg/dl ($P < 0.05$) [36]. It is interesting that sesamin reduces the liver HMG CoA and serum LDL-C level, because recent results from large-scale clinical trials of statins proved that these lipid lowering HMG-CoA reductase inhibitors have led to a revolution in the management of atherosclerosis. Statins also influence several other cellular pathways, including those involving inflammatory, oxidative, and thrombotic processes. These effects clearly have the potential to beneficially modify the atherogenic process, and it has been suggested that they contribute to the impressive results seen in the clinical trials [37]. These results suggest that sesamin's therapeutic potential may be similar to statins for atherosclerosis and warrant a large scale clinical study.

HYPOLIPIDEMIC EFFECT

Dietary sesamin and episesamin change the content and n-6/n-3 ratio of polyunsaturated fatty acid (PUFA) in rat liver and the concentrations of triglyceride (TG) and ketone bodies in serum. For 4 wk, rats were fed two types of dietary oils: (i) the control group (CO), and (ii) the AA-rich oil group (AO), with or without 0.5% (w/w) of sesame lignans (S). In

Table 2. Interaction of Sesamin and Dietary Fatty Acids on Serum and Liver Lipid Levels

	Change with sesamin from each dietary fat group			
	Linoleic acid	Palm oil	Safflower oil	Fish oil
<i>Serum lipids</i>				
Triacylglycerol				
Cholesterol				
Phospholipid				
<i>Liver lipids</i>				
Triacylglycerol				
Cholesterol	-	or -		
Phospholipid				

Rats were fed experimental diets supplemented with or without 0.2% sesamin for 15 days. Experimental diets contained 8% of either palm, safflower or fish oil and a powdered commercial chow (CE-2, Nihon Clea, Japan) contained 1% linoleic acid.

: decreased from the fat type without sesamin; : increased; -: unchanged [21, 28]

the AO group, the concentration of acetoacetate is significantly increased, but the ratio of γ -hydroxybutyrate/acetoacetate is decreased. On the other hand, the AO diet increases the concentration of TG in serum by almost twofold as compared to other groups. However, the AOS diet significantly reduces serum TG level as compared to the AO group. In addition, the AOS diet significantly increases the acetoacetate level, but reduced the γ -hydroxybutyrate/acetoacetate ratio [25].

Feeding rats with sesamin at the dietary level of 0.2% from 14 to 16 d results in an enlargement of liver weight. Ketone body production is significantly elevated in the livers perfused with oleic acid in comparison with those perfused without an exogenous-free fatty acid, and sesamin feeding causes a stimulation of ketone body production, especially when exogenous oleic acid is provided. On the other hand, the ratio of γ -hydroxybutyrate to acetoacetate, an index of mitochondrial redox potential, tends to increase in the livers perfused with oleic acid compared with those without fatty acid, thought it is consistently lowered by sesamin. The cumulative secretion of triacylglycerol, but not of cholesterol, by the livers from sesamin-fed rats is decreased markedly, especially when exogenous oleic acid is provided, suggesting an inverse relationship between the rates of ketogenesis and triacylglycerol secretion [38]. These findings suggest that dietary sesamin exerts its hypotriglyceridemic effect at least in part, through an enhanced metabolism of exogenous-free fatty acid to oxidation by promote ketogenesis at the expense of esterification into TG in rat liver.

ENHANCEMENT OF VITAMIN E LEVEL

The tocopherols, the major vitamers of vitamin E, are believed to play a role in the prevention of human aging-related diseases such as cancer and heart disease [39,40]. Tocopherol and tocotrienol are metabolized to carboxyethyl hydroxychromans [41-45]. α -tocopherol inhibits human prostate cancer cell proliferation via down-regulation of cyclin-related signaling. α -tocopherol and α -carboxyethyl hydroxychroman are effective inhibitors of PC-3 cell proliferation than α -tocopherol, α -carboxyethyl hydroxychroman, and the analogue Trolox [46]. Evidence from animal studies show that the dietary source of sesame seed, sesamin or α -tocopherol can significantly affect plasma levels of this tocopherol as well as its functional vitamin E activity [47,48]. A study has been undertaken to determine plasma levels of tocopherols in humans ($n = 9$) fed muffins containing equivalent amounts of α -tocopherol from sesame seeds, walnuts, or soy oil. Consumption of as little as 5 mg of α -tocopherol per day over a three-day period from sesame seeds, but not from walnuts or soy oil, significantly elevates serum α -tocopherol levels (19.1% increase, $p = 0.03$) and depressed plasma α -tocopherol (34% decrease, $p = 0.01$). All subjects consuming sesame seed-containing muffins detect sesamol in their plasma [49].

Tocopherol and tocotrienol are metabolized to carboxyethyl hydroxychromans by cytochrome P-450 (CYP) 3A enzyme [50,51]. Sesamin causes elevation of tissue tocopherol concentration in rats, strongly inhibits tocopherol metabolism by HepG2/C3A cells at 1.0 μ M. This may be due to the inhibition of sesamin on CYP3A-dependent

carboxychroman production and CYP4F2-dependent tocopherol- γ -hydroxylase activity [50,52]

ANTI-INFLAMMATORY EFFECT

The immune system is involved in host defense against infectious agents, tumor cells, and environmental insults. Inflammation is an important component of the early immunologic response. Inappropriate or dysfunctional immune responses underlie acute and chronic inflammatory diseases. The n-6 PUFA arachidonic acid (AA) is the precursor of prostaglandins, leukotrienes, and related compounds that have important roles in inflammation and in the regulation of immunity [53]. Feeding n-3 FA results in partial replacement of AA in cell membranes by eicosapentaenoic acid (EPA). This leads to decreased production of AA-derived mediators, through several mechanisms, including decreased availability of AA, competition for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, and decreased expression of COX-2 and 5-LOX. This is a potentially beneficial anti-inflammatory effect of n-3 FA [54]. Sesamin inhibits $\Delta 5$ desaturase activity, resulting in accumulation of dihomo- γ -linolenic acid (DGLA, 20:3, n-6), which displaces AA and consequently decreases the formation of proinflammatory 2-series prostaglandins (PGE₂). Therefore, sesamin may have a therapeutic potential similar to fish oil and blackcurrant seed oil supplementation for inflammatory diseases, such as rheumatoid arthritis [55-58].

Mice were fed for 5 weeks on a low-fat diet or on one of four high-fat diets that contained 20%, by weight, of coconut oil (CO), olive oil (OO), safflower oil (SO) or fish oil (FO). The mice were injected intraperitoneally with a non-lethal dose of LPS (100 μ g/20 g body weight) and killed 90 or 180 min later. Plasma TNF- α and IL-10 concentrations are higher 90 min post-injection than after 180 min, whereas plasma IL-1 and IL-6 concentrations are higher 180 min post-injection than after 90 min. Peak plasma TNF- α , IL-1 and IL-6 concentrations are lower in the CO- and FO-fed mice than in those fed the SO diet. Peak plasma IL-10 concentrations are higher in CO-fed mice than in those fed some of the other diets. The results indicate that the n-6 PUFA-rich SO diet produces proinflammatory cytokines in vivo and CO and FO diminish these products [59].

Another study compared the effect of 0.25% sesamin on animals with diets of 15% safflower oil (SO) (providing 12% of the added fat as linoleic acid) or 15% 2:1 mixture of linseed oil and SO (LOSO) (providing 6% γ -linolenic acid and 6% linoleic acid) for 3 weeks. Consumption of sesamin-supplemented SO+ and LOSO+ diets results in a significant increase in the levels of 20:3 n-6 (DGLA), suggesting that sesamin inhibited $\Delta 5$ desaturation of n-6 fatty acids. In animals fed LOSO diets, the levels of γ -linolenic acid, EPA and of docosahexaenoic acid (DHA) are elevated with a concomitant decrease of AA in the liver membrane phospholipids. Further, in animals fed LOSO diets with or without sesamin, an increase in the circulating levels of TNF- α is associated with a concomitant decrease in PGE₂. Despite a lack of differences in the levels of AA, the PGE₂ levels are significantly lower in mice fed sesamin-supplemented SO+ compared to those fed SO alone [19]. A study in mice fed diets supplemented with 5% safflower oil

(SO) in the absence or presence of 1% sesamol is similar to the result of sesamin. Sesamol or its metabolite can inhibit the *in vivo* Δ 5 desaturation of n-6 fatty acids. In animals fed sesamol supplemented SO diets, the levels of PGE₂ (228 ± 41 pg/ml) are markedly lower (P<0.01) compared to those fed SO diet alone (1355 ± 188 pg/ml). Concomitantly, the concentrations of IL-6 are also lower (P<0.01) in mice fed sesamol diet (63 ± 11 ng/ml) compared to the controls (143 ± 22 ng/ml) [60].

The effects of continuous tube feedings of emulsions containing safflower oil or linseed oil with sesamin (SO+ and LO+) or without sesamin (SO and LO) are examined by whole blood from rats. A significant accumulation of DGLA only in the liver phospholipids of animals fed SO+ and LO+. These changes are associated with significant reductions in plasma PGE₂ concentrations in animals fed SO+ compared with those fed SO (P: < 0.05). Plasma concentrations of TNF- α are significantly lower (P: < 0.05) in the animals fed LO+ than in those fed SO (199 ± 48 and 488 ± 121 ng/L, respectively). These results indicate that in rats, tube feedings of diets containing sesamin exerted anti-inflammatory effects [61].

A study compares the effect of diets containing sesame oil (SSO) or both SSO and Quil A, a saponin that emulsifies fats and potentiates the immune responses in mice. A mixture of oils having a fatty-acid composition similar to that of SSO served as a control diet. The levels of docosapentaenoic acid in mice fed Quil-A-supplemented diets and of DGLA in those fed SSO diets are markedly higher in the liver. These changes are associated with a significant reduction in the plasma PGE₍₁₊₂₎ and thromboxane-B₂ levels in response to an intraperitoneal injection of a lethal dose of LPS (LD₅₀ 20 mg/kg). The levels of IL-6 are elevated and those of IL-1 are decreased in mice consuming Quil-A-supplemented diets. The IL-10 levels that are elevated in all mice after LPS exposure, remains higher (even at 9 h) only in those fed Quil-A-supplemented diets, but declined rapidly in others. During a 48-hour observation period following LPS injection, all control animals died, and survival is 40% in the SSO group, and 27 and 50%, respectively, in those fed Quil-A-supplemented control and SSO+ Quil-A diets [18].

Nutritional-induced hypercholesterolaemia in New Zealand rabbits causes increased susceptibility to experimental infections. Rabbits fed cholesterol (0.5 g%) for 8 weeks are injected intravenously with varying doses of LPS (3-100 µg/kg). LPS induced higher serum TNF- α levels in hypercholesterolaemic rabbits than in normal rabbits or rabbits fed with chow containing sesame oil. TNF- α levels rose faster in hypercholesterolaemic rabbits than in normal rabbits, reaching maximum levels at 60 min and 120 min, respectively, after LPS injection. The survival rate of hypercholesterolaemic rabbits (1/11) is lower than in normal rabbits (6/7) or rabbits fed with the sesame oil chow (4/4) at the higher LPS doses. No death occurred at lower doses. Sesame oil protects the hypercholesterolaemic rabbits by lower the TNF- α secretion [35].

Sesamin protects mice from cecal ligation and puncture. After cecal ligation and puncture in female mice, only 20% of the controls and as many as 65% in the sesamin+ safflower oil (SO+) group survived. The levels of cytokines and

dienoic eicosanoids produced in response to an intraperitoneal injection of a nonlethal LPS dose (50 µg/mouse) are measured in both groups. The IL-10 levels are markedly higher in mice fed SO+ diets compared with the controls. However, the plasma concentrations of PGE₁₊₂, TNF- α , IL-6, and IL-12 do not differ significantly between the two groups of mice [62].

In the experimental study using a rat burn model, n-6 PUFA increased serum TNF- α , IL-6 and decreased nitrogen balance (NB) (P < 0.05), when compared with a fat-free control. But addition of n-3 PUFA reduced TNF- α and IL-10 (P < 0.05) and improved NB (P < 0.05). Patients underwent surgery for esophageal cancer fed by total parenteral nutrition with soybean oil emulsion, their serum IL-6 significantly increased at 2 and 6 h after operation. Oral/enteral supplementation of EPA ethyl ester (1.8 g/d) significantly reduced the postoperative IL-6 production (P < 0.05 at 1, 2, and 6 h after operation), and improved cell-mediated immune function 3 wk after operation (P = 0.05). During the chemoradiation therapy, cell-mediated immune function is improved significantly in the patients fed enterally with EPA ethyl ester (n = 5), when compared with the patients without EPA (n = 14) [63]. Since sesamin inhibits Δ 5 desaturase activity, resulting in accumulation of DGLA, which displaces AA and consequently decreases PGE₂, TNF- α and IL-6, it is likely that sesamin may be useful for these clinical applications [54,60,62].

FATTY ACID OXIDATION AND PPAR

Peroxisome proliferators are a diverse group of rodent hepatocarcinogens that include hypolipidemic drugs, plasticizers and herbicides. These compounds when administered to rats and mice produce a dramatic increase in the size and number of hepatic peroxisomes and increase the capacity of the hepatocyte to metabolise fatty acids by inducing peroxisomal α -oxidation enzymes such as acyl CoA oxidase. Members of the steroid hormone receptor superfamily of ligand-activated transcription factors have been identified that can be activated by peroxisome proliferators and are therefore called peroxisome proliferator activated receptors (PPAR). There appear to be four PPAR isoforms within vertebrates termed α , β , γ , and δ and the isoform α appears to be the one that is most strongly activated by synthetic peroxisome proliferators such as Wy-14,643 [64]. PPARs control the expression of genes implicated in intra- and extracellular lipid metabolism, most notably those involved in peroxisomal α -oxidation. PPARs are activated by a wide range of fatty acids and hypolipidemic drugs, such as clofibrate, that lower triglyceride levels in man [64,65]. The hypotriglyceridemic action of fibrates and certain fatty acids also involves PPAR. This action is related with: 1) increased hydrolysis of plasma triglycerides due to induction of LPL and reduction of apoC-III expression; 2) stimulation of cellular fatty acid uptake and conversion to acyl-CoA derivatives due to increased expression of genes for fatty acid transport protein and acyl-CoA synthetase; 3) increased peroxisomal and mitochondrial beta-oxidation; and 4) decreased synthesis of fatty acids and triglycerides and decreased production of very low density lipoprotein (VLDL) [65].

Sesamin dose-dependently increases both mitochondrial and peroxisomal palmitoyl-CoA oxidation rates [26,28]. Mitochondrial and peroxisomal activities are increased in rats fed a 0.5% sesamin diet in relation to rats on the sesamin-free diet. Dietary sesamin greatly increased the hepatic activity of fatty acid oxidation enzymes, including carnitine palmitoyltransferase, acyl-CoA dehydrogenase, acyl-CoA oxidase, 3-hydroxyacyl-CoA dehydrogenase, enoyl-CoA hydratase, and 3-ketoacyl-CoA thiolase. Dietary sesamin also increased the activity of 2,4-dienoyl-CoA reductase and $^3, ^2$ -enoyl-CoA isomerase, enzymes involved in the auxiliary pathway for ω -oxidation of unsaturated fatty acids dose-dependently. Sesamin increases the gene expression of mitochondrial and peroxisomal fatty acid oxidation enzymes. Among enzymes affected by sesamin the most are peroxisomal acyl-CoA oxidase and bifunctional enzyme gene expression [26,30]. Therefore, the alteration in hepatic fatty acid metabolism through PPAR may account for the serum lipid-lowering effect of sesamin in rats.

PPARs consist of three members: PPAR α , PPAR β , and PPAR γ . Among them, PPAR γ is essential for controlling thermogenesis and adipocyte differentiation. The ligands for PPAR γ include 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂)-a metabolite from the prostaglandin synthesis pathway, and glitazones--drugs utilized in the treatment of patients with diabetes. The precursors for prostaglandins are fatty acids consumed from diet and these precursors have long been postulated to have a regulatory role in immune functions. PPAR γ and its ligands (15d-PGJ₂, troglitazone) are important for the modulation of immune and inflammatory reactions, such as TNF- α and NO productions [66,67]. They are also participating factors for Th1/Th2 T helper cells and NK cells differentiation and development [68].

Activation of PPAR γ by gemfibrozil, a lipid-lowering drug, can inhibit cytokine-induced production of NO and the expression of inducible NO synthase (iNOS) in human U373MG astroglial cells and primary astrocytes [69]. Using the carrageenan-induced paw edema model of inflammation, PPAR agonists hinder the initiation phase, but not the late phase of the inflammatory process. Despite the fact that exclusive effects on PPARs have been questioned, the bulk of evidence suggests that all three PPAR subtypes, PPAR α , PPAR β , PPAR γ , play a significant role in controlling inflammatory responses [70].

NEUROPROTECTIVE EFFECT

Microglia, a resident macrophage-like population of brain cells, have been proposed to play a role in host defense and tissue repair in the CNS. However, microglia have also been proposed to play a pathogenetic role in immunologically mediated CNS diseases, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease [71]. Nitric oxide, cytokine, and reactive oxygen species (ROS) released from activated microglia and other glial cells may participate in the neurodegenerative process [72]. Nitric oxide has pleiotropic effects in the CNS [73], excessive NO production in the CNS can be toxic to many different cell types, including astrocytes and neurons [74-76]. The inducible nitric oxide synthase (iNOS), is rapidly transcribed and

expressed in microglia and astrocytes after stimulation with LPS, cytokines and amyloid [77,78].

LPS binding to the Toll-like receptor 4 (TLR4) activates a complex array of intracellular signaling pathways involving tyrosine kinases, mitogen-activated protein (MAP) kinases: p38 mitogen-activated protein kinase (MAPK) and c-jun N-terminal kinase (JNK), but not extracellular signal-regulated kinase (ERK1/2) and NF- κ B mediated cytokine gene expression [79-81]. LPS induces the release of TNF- α from microglia and facilitate TNF- α or NO-mediated neuron death in vitro [82,83]. Gemfibrozil, a PPAR γ agonist, inhibits the IFN- γ -induced iNOS probably by inhibiting the activation of nuclearfactor- κ B (NF- κ B), activator protein-1 (AP-1), and CCAAT/enhancer-binding protein (C/EBP β) [69].

Neuroprotective antioxidants have properties of nitric oxide synthase inhibition. Silymarin, quercetin, baicalin and resveratrol at a micromolar range suppressed iNOS gene expression and NO production in microglial cell line BV-2 and macrophage RAW 264.7 after stimulation with LPS [82,84]. Sesamin and sesamol significantly inhibited LPS-stimulated TNF- α , IL-6 and NO productions, iNOS mRNA and protein expression in BV-2 microglia [85,86]. Gemfibrozil, an activator of PPAR γ , inhibits the induction of iNOS [69]. Since three PPAR α , PPAR β , PPAR γ , play a role in controlling inflammatory responses, sesamin may exert its action through activation of PPARs. Further studies are needed to confirm the activation of PPARs by sesamin using transfection or ligand-binding assays [65,75].

Furthermore, sesamin and sesamol were able to inhibit H₂O₂-induced ROS generation in BV-2 cells and in cell-free condition. Excessive NO and ROS production in the brain are believed to contribute to neurodegenerative processes and polyphenolic compounds that inhibit the NO production may have neuroprotective potential [87]. Sesamin and sesamol at concentrations of 50-100 μ M inhibited 70 to 95% of LPS-stimulated iNOS mRNA expression and NO production in BV-2 microglia. Sesamol, but not α -tocopherol, only inhibited 50% of iNOS mRNA expression. The reduction in LPS-induced IL-6 and iNOS protein expression by sesamin and sesamol were proportional to their reduction of IL-6 and iNOS mRNA. The decrease of IL-6 and iNOS protein by sesame lignans is due to a decrease in the transcription and translation of the IL-6 and iNOS genes [85,86]. The mechanism of inhibition of LPS-induced iNOS expression by sesame lignans may be similar to other agents that selectively inhibit p38 MAPK [85,88].

P38 MAPK is thought to mediate inflammatory responses in various cell types, possibly through the activation of transcription factors that positively regulate induction of inflammatory genes [89]. Inhibition of p38 MAPK can be expected to be beneficial in injuries involving microglia activation and inflammation. Specific inhibitors of p38 MAPK have been proven to reduce inflammation, slow down microglia activation and provide neuroprotective effects [90]. Compounds that inhibit p38 MAPK activation in microglia show potential anti-inflammatory effects and protect neurons against excitotoxicity or LPS-induced neurotoxicity [82,91]. LPS induces the activation of p38 and JNK, but not ERK1/ERK2 MAPK in BV-2 microglia. The phosphorylation of p38 increased with time, reaching a maximum between 15 and 20 min. Sesamin and sesamol

significantly suppressed LPS-induced p38 MAPK expression (60 to 75%), followed by sesamol (30%). In contrast, -tocopherol had no effect on LPS-induced p38 MAPK activation. The results of p38 MAPK inhibition by sesamin and sesamol correlated very well with their effects on iNOS/NO inhibition. P38 MAPK inhibitor, SB203580, dose-dependently inhibited NO production in LPS-stimulated BV-2 microglia; further support the role of p38 MAP kinase in NO production. The mechanisms of sesame antioxidant inhibition of the LPS-induced IL-6 and iNOS mRNA/protein involve the p38 MAPK signal pathway and/or antioxidative activity [85,86]. Whether sesamin act on these PPAR subtypes remains to be elucidated [30]. Further studies are required to confirm these activities on the MAPK signaling pathway and therapeutic potential in neuroprotection.

EFFECT OF SESAMIN ON HYPOXIC AND OXIDATIVE STRESSES

Hypoxia/ischemia is a pathophysiological condition characterized by an increase in reactive oxygen species (ROS) and a change in the intracellular redox level. Altered cellular

oxidation and impaired cellular function occur in stroke and many neurodegenerative diseases including Alzheimer’s and Parkinson’s diseases [92,93]. The cellular response to hypoxia may provide important clues about impaired cellular function and neuronal cell death [94]. Reactive oxygen species have been proposed to act as second messengers in redox-sensitive signal transduction pathways and can also damage biomolecules [93]. Reactive oxygen intermediates (ROS; superoxide radical, O₂⁻; hydrogen peroxide, H₂O₂; hydroxyl radical, ·OH), are mainly produced in mitochondria. ROS act as physiological modulators of some mitochondrial functions, but may also damage mitochondria. Oxygen derived radicals are implicated in lipid peroxidation events, and are critical in neuronal injury following ischemia/hypoxia [95,96]. Antioxidants may have the potential to protect cells from oxidative damage [97,98]. Sesame lignans suppress lipid peroxidation of erythrocytes [99], Sesamin and sesamol preventing hypoxic or H₂O₂-stressed death of neuronal PC12 cells [15]. Hypoxia causes the activation of several MAPKs: ERK1/2, JNK and p38 MAP kinase signaling pathways [100,101]. Sesamin and sesamol suppress ROS, ERK1/2, JNK and p38 MAPKs and caspase-3 correlated well with the reduction in LDH

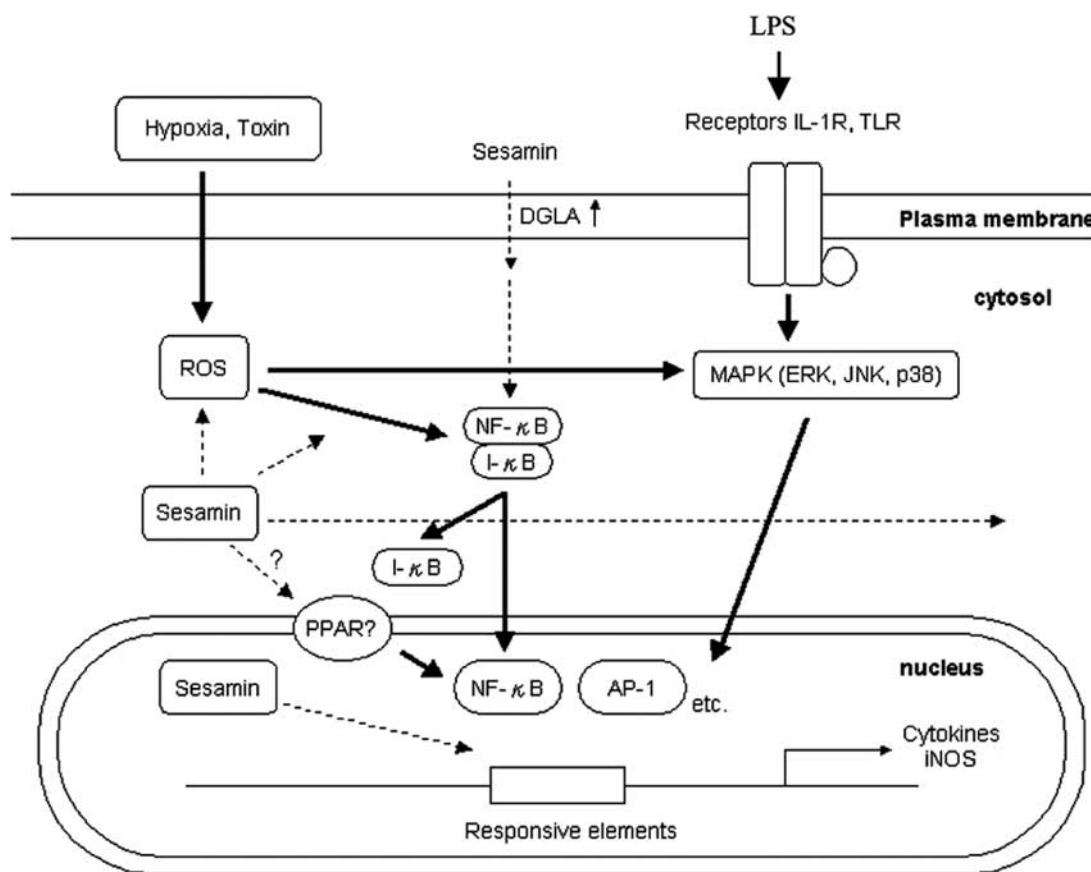


Fig. (2). Mechanism of sesamin on signal transduction pathway.

Hypoxia/ischemia causes an increase in ROS and a change in the intracellular redox level. Sesamin partially prevents hypoxic or H₂O₂-stressed neuronal injury. Hypoxia causes the activation of several MAPKs: ERK1/2, JNK and p38 MAP kinase signaling pathways. Sesamin suppresses cytokine and ROS production, ERK1/2, JNK, and p38 MAPKs and, caspase-3 activation that correlated well with the reduction in LDH release from cells under hypoxia. LPS binding to the Toll-like receptor 4 (TLR4) activates a complex array of intracellular signaling pathways involving tyrosine kinases, MAPKs and NF-κB mediated cytokine and iNOS gene expressions. Sesamin significantly inhibits LPS-stimulated cytokine and iNOS mRNA and protein expression in BV-2 microglia. It remains unclear whether sesamin also exert its action through activation of PPARs [14-15,85-86].

release from PC12 cells under hypoxia [15, 102]. Sesamin and sesamol also protect BV-2 microglia from hypoxia-induced cell death. They dose-dependently reduce hypoxia-induced lactate dehydrogenase (LDH) release and dichlorofluorescein (DCF)-sensitive ROS production. Sesamin or sesamol reduces caspase-3 and MAPK activation correlated well with diminished LDH release in BV-2 cells under hypoxia [14]. Furthermore, they preserved superoxide dismutase (SOD) and catalase activities in PC12 and BV-2 cells under hypoxia or H₂O₂-stress [14,15].

ANTIOXIDANT EFFECT

H₂O₂ and superoxide (O₂⁻) are both produced in a number of cellular reactions, including the iron-catalysed Fenton reaction, and by various enzymes such as lipoxygenases, peroxidases, NADPH oxidase and xanthine oxidase. Consequences of hypoxia-induced oxidative stress depend on tissue and/or species (i.e. their tolerance to anoxia), on membrane properties, on endogenous antioxidant content and on the ability to induce the response in the antioxidant system. The formation of ROS is prevented by an antioxidant system: antioxidants (ascorbic acid, glutathione, tocopherols), enzymes regenerating the reduced forms of antioxidants, and ROS-interacting enzymes such as SOD, peroxidases and catalases. In plants, many phenolic compounds (in addition to tocopherols) are potential antioxidants: flavonoids, tannins and lignin precursors may work as ROS-scavenging compounds [reviewed in 103]. Studies have suggested the beneficial effects of antioxidant nutrients such as vitamin E, green tea extract, ginkgo biloba extract, resveratrol and niacin in cerebral ischemia and recirculation brain injury. These results are important in light of an attenuation of the deleterious consequences of oxidative stress in ischemia and recirculation injury [98]. For instance, silymarin is a polyphenolic flavonoid derived from milk thistle that has anti-oxidant, anti-inflammatory, cytoprotective and anticarcinogenic effects [104]. Silymarin significantly reduces the LPS-induced nitrite, iNOS mRNA and protein levels in microglia. It also reduces the LPS-induced superoxide generation and nuclear factor B (NF- κ B) activation [82]. The abilities of 15 flavonoids as a scavenger of ROS (hydroxyl radical and superoxide anion) are compared. Hydroxyl radical (\cdot OH) is generated by the Fenton system, and assayed by the determination of methanesulfonic acid (MSA) formed from the reaction of dimethyl sulfoxide (DMSO) with \cdot OH. Catechin, epicatechin, 7,8-dihydroxy flavone, and rutin show the \cdot OH scavenging effect 100-300 times superior to that of mannitol, a typical \cdot OH scavenger. The other flavonoids show no \cdot OH scavenging effect at their concentrations up to 50 μ M. Baicalein, quercetin, morin, and myricetin unexpectedly increased the \cdot OH production in the Fenton system [105]. Sesame lignans are antioxidants but show pro-oxidant effects when their concentrations up to 100 μ M [14,15]. Sesamin and sesamol, with two methylenedioxy bridges have potentially 4 functional OH groups, and scavenged ROS in cell-free condition better than sesamol with 2 OH groups. This suggests that the higher inhibition of LPS-induced NO production by sesamin and sesamol may be due to the difference in numbers of functional OH group [85]. A water-soluble form of sesamol, 1,2,4-benzenetriol, has a similar

potency in inhibiting LPS-induced NO production (our unpublished observation). The methylenedioxy bridge of sesamin and sesamol, is formed by a redox reaction of cytochrome P450 in the presence of O₂ and NADPH [106]. Sesamin is metabolized in the liver and converted to an antioxidative form that inhibits superoxide production in aortic endothelium [107]. The metabolized forms of sesamin show stronger scavenging activity than sesamin against ROS in O₂⁻, \cdot OH, 2,2-diphenyl-1-picrylhydrazyl radical (DPPH \cdot) and TBARS assay [108]. However, the free radical scavenging power of sesame crude extract by the DPPH \cdot assay shows the order: sesamin> sesamol> sesaminol triglucoside>sesaminol diglucoside [109]. Using DPPH \cdot kinetic model to study the free radical scavenging capacity, the second-order rate constant k₂ values of the sesame antioxidants are calculated for the quenching reaction with DPPH \cdot radical. The k₂ values are in the order sesamol>sesamol dimmer>sesamin> sesamol> sesaminol triglucoside>sesaminol diglucoside [110].

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