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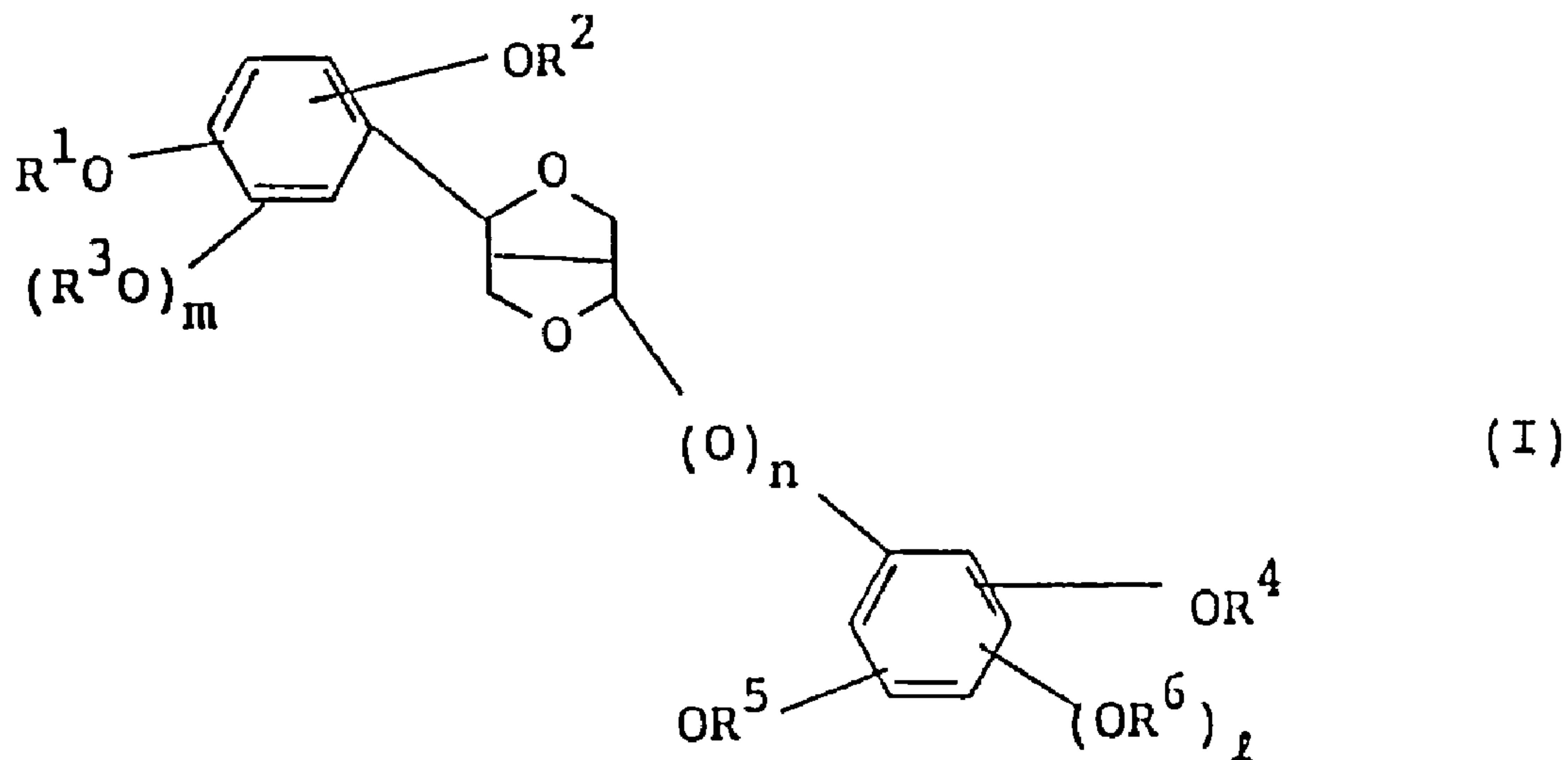
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(54) **AGENT REDUISANT LE TAUX DE CHOLESTEROL OU DE
GRAISSE NEUTRE**

(54) **CHOLESTEROL OR NEUTRAL FAT LEVEL REDUCER**

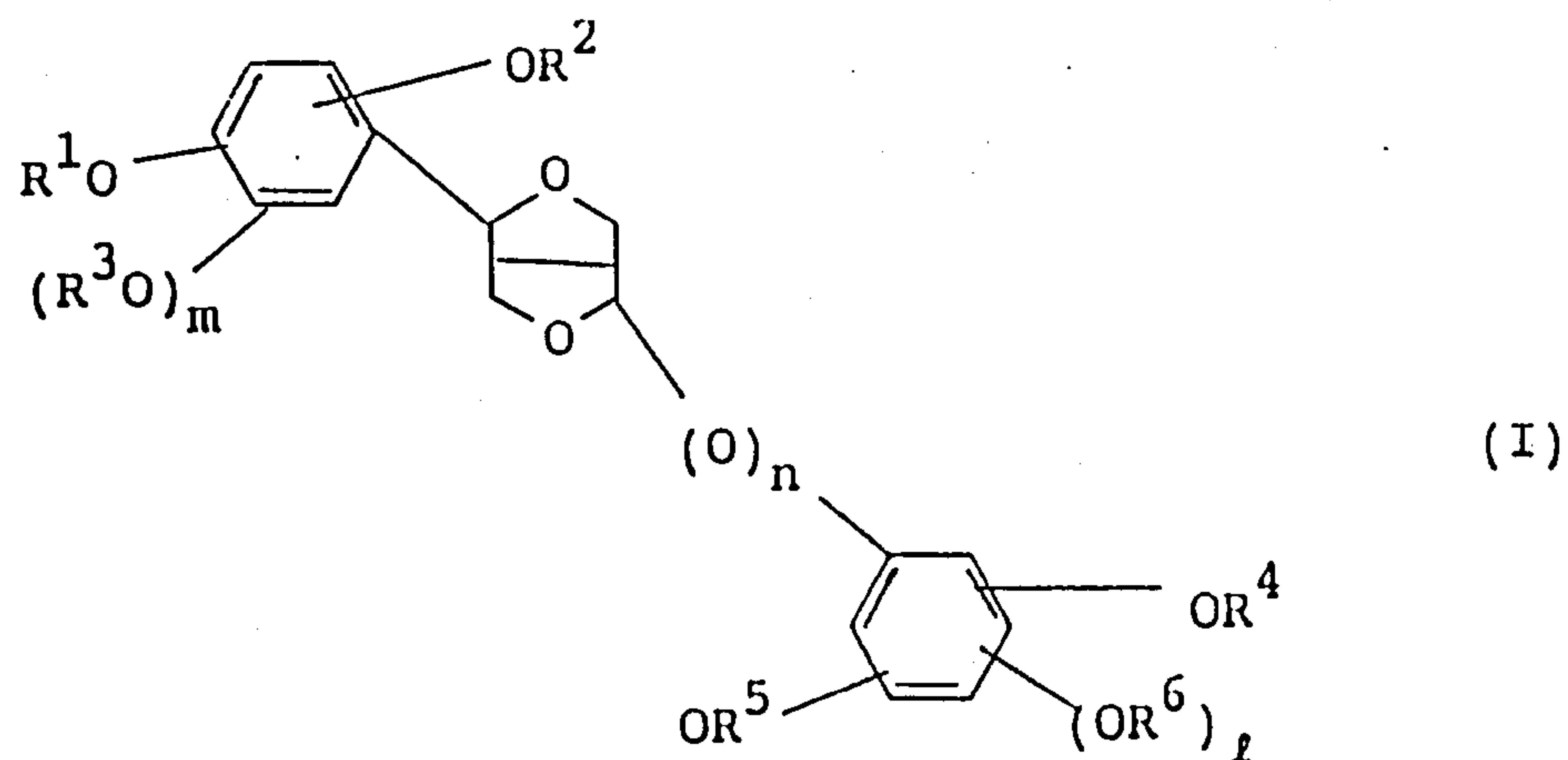


(57) A cholesterol or neutral fat level reducer comprises, as active ingredient, a dioxabicyclo- [3.3.0]octane derivative having the general formula (I): (I) wherein R¹, R², R³, R⁴, R⁵ and R⁶ independently represent a hydrogen atom or an alkyl having 1 to 3 carbon atoms, or R¹ and R² and/or R⁴ and R⁵ together form a methylene group or an ethylene group, and n, m and l are 0 or 1.



ABSTRACT

A cholesterol or neutral fat level reducer comprises, as active ingredient, a dioxabicyclo-[3.3.0]octane derivative having the general formula (I):



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 independently represent a hydrogen atom or an alkyl having 1 to 3 carbon atoms, or R^1 and R^2 and/or R^4 and R^5 together form a methylene group or an ethylene group, and n , m and l are 0 or 1.

This application is a division of Canadian patent application No. 2,021,714 filed July 20, 1990 and relating to a liver function improver comprising, as an effective ingredient, a dioxabicyclo[3.3.0]octane derivative, and to a food or drink containing same. The present divisional application is directed to a cholesterol or neutral fat level-reducer comprising, as an active ingredient, such a derivative.

The liver is the largest substantial organ of a human body, in addition to the brain, and has various functions such as a detoxifying action, carbohydrate metabolism, protein metabolism, the formation and secretion of bile, the formation of blood coagulation factors, hormone-controlling action, and the action of storing various living body constituents such as fat, glycogen, proteins and vitamins. These functions are acutely or chronically impeded by viruses, drugs, poisons, excessive intake of alcohol, malnutrition, liver circulatory system troubles, bile duct occlusion and the like, and as a result, there appear such diseases as viral hepatitis, drug toxic hepatitis, alcoholic hepatitis, congestive hepatitis, liver disorder due to a stagnation of hepatic juice fatty liver, interus, and finally, hepatocirrhosis.

For example, to remedy liver disorder caused by alcohol, there has been adopted not only a method of controlling an intake of meat fat and an excessive intake of alcohol, but also a medicinal therapy using antihistamic agents, barbituric acid salts, adenosine triphosphate (ATP), pyrazole, a mixture of dihydroxy acetone and riboflavin, glucuronic acid, arginine hydrochloride, and amino acid preparations such as glutathione. Nevertheless, the effects of these drugs are not satisfactory, and there is no certain remedial method other than a

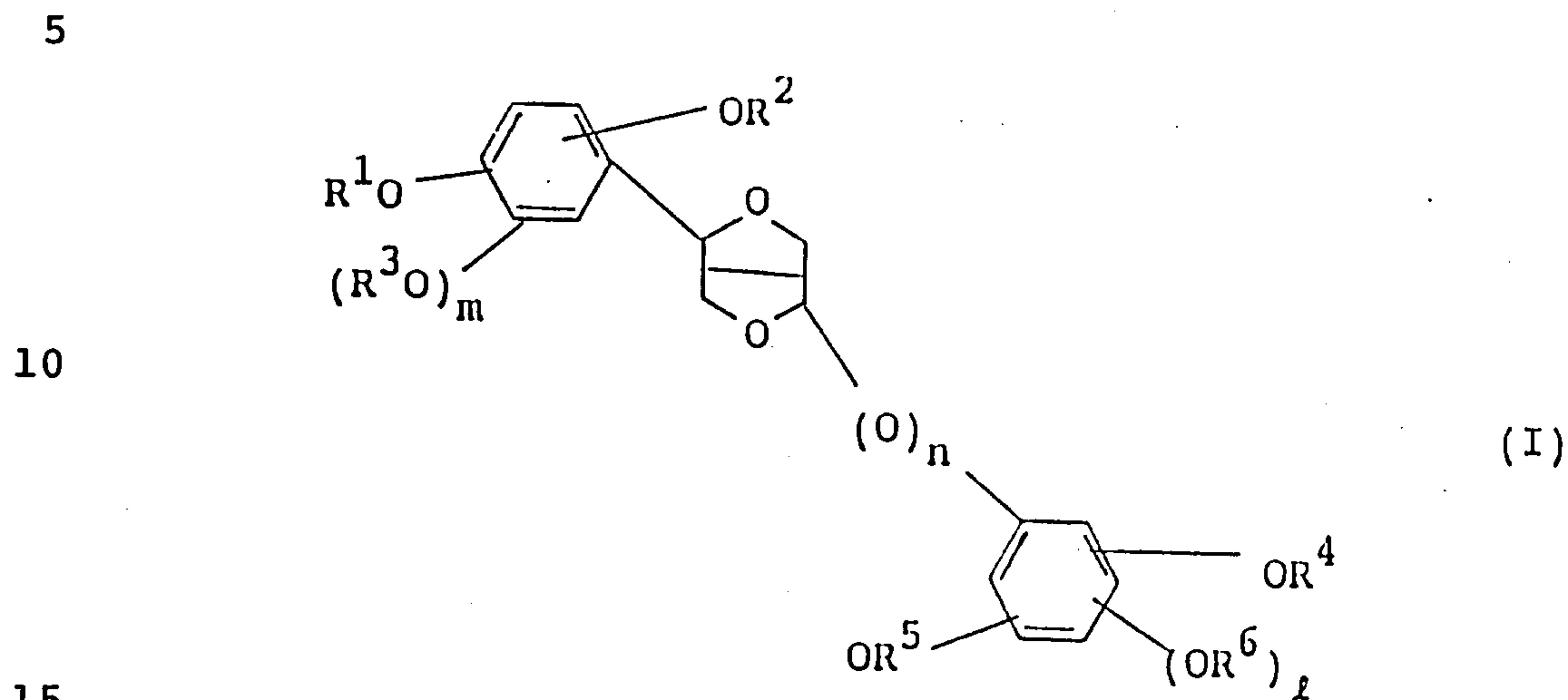
control of an excessive intake of alcohol. As one of the causes of liver disorder brought on by drugs and poisons, there can be mentioned the formation of a harmful oxygen free radical, and accordingly, a large quantity of glutathione is administered for therapy of toxicoses and allergic diseases. Especially, for a protection of cells, glutathione reduces or extinguishes an active oxygen species or free radical by glutathione peroxidase, or glutathione reacts with a poison through glutathione-S-transferase and discharges the poison from cells in the form of a glutathione conjugate, to exert the intended function whereby anti-oxidation, detoxification and a protection from radiation damage can be achieved. Nevertheless, even if glutamine per se is administered, the half-life is short (only several minutes) and tissue glutathione is not effectively increased. Accordingly, the development of glutathione derivatives and the like is now under investigation.

Under the above circumstances, however, the development of a novel liver function improver is urgently required.

Since the liver-derived enzyme activity (glutamic-oxaloacetic aminotransferase (GOT) and glutamic-pyruvic aminotransferase (GPT)] in sera of mouse and rat is increased by liver disorder, the inventors searched for a liver function improver by using GOT and GPT as indications, and as a result, found that a dioxabicyclo[3.3.0]octane isolated from sesame seeds, sesame lees, and sesame oil, or a synthesized dioxabicyclo[3.3.0]octane derivative, has a liver function-improving action, a cholesterol level-reducing and a neutral fat level-reducing action, and is very safe.

In accordance with the present invention, there is thus provided a liver function improver

comprising, as active ingredient, a dioxabicyclo-[3.3.0]octane derivative having the general formula (I):



wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 independently represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or R^1 and R^2 and/or R^4 and R^5 together form a methylene group or an ethylene group, and n , m and ℓ are 0 or 1.

The present invention also provides, in another aspect thereof, a cholesterol or neutral fat level reducer comprising, as active ingredient, a dioxabicyclo[3.3.0]octane derivative of formula (I) as defined above.

According to a further aspect of the present invention, there is provided a food containing the above derivative of formula (I).

30 Examples of suitable dioxabicyclo[3.3.0]-octane derivatives of formula (I) which may be in accordance with the present invention include sesamin, sesaminol, episesamin, episesaminol, sesamol, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo-
35 [3.3.0]octane and 2-(3,4-methylenedioxyphenyl)-6-(3-

methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]-octane can be used. These derivatives can be used alone or in the form of a mixture of two or more thereof.

5 The derivatives of formula (I) and extracts composed mainly of a derivative of the formula (I) can be obtained according to the following procedures. First, an extract composed mainly of a derivative of formula (I) can be
10 obtained from sesame oil according to a method comprising extracting sesame oil with an organic solvent substantially immiscible with sesame oil and capable of extracting and dissolving the derivative of formula (I), and concentrating the extract. As
15 the organic solvent, there can be mentioned, for example, acetone, methylethylketone, diethylketone, methanol and ethanol. For example, an extract composed mainly of a derivative of formula (I) can be obtained by mixing sesame oil homogeneously with
20 an organic solvent as mentioned above, allowing the mixture to stand at a low temperature, carrying out a phase separation according to a customary process, and removing the solvent from the solvent fraction by evaporation. More specifically, sesame oil is
25 dissolved in 2 to 10 volumes, preferably 6 to 8 volumes of acetone, and the solution is allowed to stand at -80°C overnight. As a result, the oil component is precipitated, and the organic solvent is removed from the obtained filtrate by
30 distillation, whereby an extract composed mainly of the derivative of formula (I) is obtained. Alternatively, sesame oil is mixed with hot methanol or hot ethanol, the mixture is allowed to stand at room temperature, and the solvent is removed from
35 the solvent fraction to obtain an extract composed mainly of the derivative of formula (I). More specifically, sesame oil is mixed with hot methanol

(higher than 50°C) or hot ethanol (higher than 50°) in a volume 2 to 10 times, preferably 5 to 7 times, as large as the volume of the sesame oil to effect a violent extraction. The phase separation is effected
5 by a phase separation when standing at room temperature or a centrifugal separation according to customary procedures, and the solvent is removed from the solvent fraction by distillation to obtain an extract composed mainly of the derivative of
10 formula (I). Furthermore, the supercritical gas extraction can be utilized. The derivative of formula (I) can be obtained from an extract as mentioned above by treating the extract by a customary method such as column chromatography, high
15 performance liquid chromatography, recrystallization, distillation, or liquid-liquid counter-current distribution chromatography. More specifically, by using a reversed phase column (5C₁₈) and methanol/water (60/40) as the eluent, the
20 extract is subjected to high performance liquid chromatography, the solvent is removed by distillation, and the obtained crystal is recrystallized from ethanol to obtain a derivative of formula (I), such as sesamin, episesamin,
25 sesaminol or episesaminol. The sesame oil used in the present invention can be either a purified product or a crude product. Furthermore, sesame seeds or sesame lees (defatted sesame seeds having a residual oil content of 8 to 10%) can be used. In
30 this case, sesame seeds or sesame lees are pulverized if necessary, and then subjected to the extraction according to customary procedures using any solvent, for example, a solvent as mentioned above with respect to the extraction from sesame
35 oil. The extraction residue is separated, and the solvent is removed from the extract by evaporation or the like to obtain an extraction product. The

derivative used in accordance with the present invention, for example, sesamin, sesaminol, episesamin, episesaminol, sesamolin, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane or 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]octane, can be obtained from a sesame seed extract, a sesame lee extract or a crude sesame oil extract according to the same procedures as described above. Moreover, the derivative can be obtained from a by-product formed in the sesame oil-preparing process.

The process for the purification of the derivative of formula (I) and the process for obtaining the extract are not limited to those mentioned above, and the derivative used in accordance with the present invention and the extract composed mainly of such a derivative are not limited to those obtained from sesame oil, sesame lees and sesame seeds, but as is apparent to persons with ordinary skill in the art, all natural substances containing a derivative of formula (I) can be used. For example, there can be mentioned Acanthopanax sessiliflorus, paulowina, Ginkgo-biolobu and Piper lonum.

The following processes can be adopted for the synthesis of the derivatives of formula (I).

For example, sesamin and episesamin can be synthesized according to the process of Beroza et al. [J. Am. Chem. Soc., 78, 1242 (1956)]. Pinoresinol [in the general formula (I), R^1 and R^4 represent H, R^2 and R^5 represent CH_3 , and n, m and ℓ are zero] can be synthesized according to the process of Freudenberg et al. [Chem. Ber., 86, 1157 (1953)]. Furthermore, syringaresinol [in the general formula (I), R^1 and R^4 represent H, R^2 , R^3 , R^5 and

R⁶ represents CH₃, n is zero, and each of m and l is 1) can be synthesized according to the process of Freundenberg et al. [Chem. Ber., 88, 16 (1955)].

5 The derivatives of formula (I) can also be used in the form of a glycoside. Furthermore, these derivatives can be used alone or in combination with other liver function improvers or a functional factor of a food.

10 The liver function improver of the present invention can be orally administered, or non-orally administered, for example, by intramuscular injection, hypodermic injection or intravenous injection.

15 The dosage depends on the state of a person to whom the liver function improver is administered, but in general, in the case of the oral administration, the dosage is 1 to 100 mg/day, and in the case of the non-oral administration, the dosage is 0.1 to 20 mg/day. For the preparation of an injection, a solubilizing agent for a drug, for example, a nonionic surface active agent, can be used. More specifically, the derivative of formula (I) is dissolved under heating in a nonionic surface active agent such as POE(60) hardened castor oil or POE sorbitan-monooleate in a volume 80 times as large as the volume of the derivative of formula (I), and the solution is diluted with a physiological saline to form an injection solution. An isotonic agent, a stabilizer, an antiseptic agent, and an analgesic agent, can be incorporated according to need. If necessary, the derivative of formula (I) can be formed into an emulsion, a capsule, a dust, a granule or a tablet.

35 In view of the cholesterol level-reducing action and the neutral fat level-reducing action, it is considered preferable to incorporate the derivative of formula (I) into foods containing oil and fat, although the kind of food into which the

derivative of formula (I) is incorporated is not limited. For example, there can be mentioned natural foods such as meat, fish and nut, foods to which oil and fat are added at the cooking step, such as
5 Chinese meals, Chinese noodles and soups, foods cooked by using oil and fat as the heating medium, such as Japanese fried foods, fried bean curd, Chinese fried rice, doughnuts and fried dough cakes, oil and fat foods or processed foods to which oil
10 and fat are added at the processing step, such as butter, margarine, mayonnaise, dressings, chocolate, instant noodles, caramels, biscuits and ice creams, and foods onto which oil and fat are sprayed or coated at the processing step, such as sliced and
15 dried rice cakes, hard biscuits and bean-jam buns. Since the extract composed mainly of the derivative of formula (I) comprises effective ingredients inherently contained in an edible oil and fat or extracts thereof, addition of the extract of the
20 present invention can be easily accomplished and the extract of the present invention can be easily added to the above-mentioned foods. Note, the foods are not limited to oil- or/and fat-containing foods, and the extract of the present invention can be added to
25 all foods to provide foods having a liver function-improving action, a cholesterol level-reducing action, and a neutral fat level-reducing action.

In the present invention, the amount of the derivative of formula (I) is not particularly
30 critical, but preferably the amount of such a derivative is 0.001 to 20% by weight, especially 0.01 to 10.0% by weight, based on the food to which the derivative is added. If the amount of the derivative of formula (I) is smaller than 0.001% by
35 weight, the effect is low, and if the amount is larger than 20% by weight, the taste and flavor of some foods are adversely affected. Preferably, the

content of the derivative in the extract is at least 25%. Moreover, the derivative of formula (I) can be converted to a cyclodextrin inclusion compound and the formed powder can be used.

5 The significance of the present invention will now be described. Butter is a very popular food prepared from butter fat or cream, a milk solid and a natural colorant, and further, contains sodium chloride. The fat content in butter is usually about
10 80%. For the preparation of butter, cream obtained by centrifugal separation is subjected to stirring (churning) directly or after lactic acid fermentation, whereby the fat globule membrane is destroyed and fat is fused into particles, and sodium chloride
15 is added to the churned cream and kneading (working) is carried out to obtain a product having a homogeneous texture. The thus-prepared butter is a popular food because of its peculiar and characteristic taste and flavor, but since butter has a very high
20 cholesterol content (the cholesterol level is about 220 mg/100 g) health experts recommend eliminating butter from a food or reducing the content of butter for lowering or controlling the intake of cholesterol. If the derivative of formula (I) or the
25 extract composed mainly of such a derivative is added to butter, an effect of preventing the increase of the cholesterol level after the intake of butter can be obtained. Moreover, since the product of the present invention is not an imitation
30 food, the inherent taste and flavor of butter can be retained. The derivative of formula (I) or the extract composed mainly of such a derivative can be added at any step of the butter-preparing process, but the addition at the kneading operation (working)
35 is especially preferable.

The present invention also can be applied to the improvement of a food quality. Mayonnaise is

prepared by mixing edible oil with vinegar by using egg yolk lecithin as an emulsifier, and sugar, table salt, mustard and white pepper are used as additives. Mayonnaise and dressings are o/w type emulsions in which the water layer is a main component, and according to JAS standards, mayonnaise is defined as a product having an oil content, which is formed by using an egg as the emulsifier, and dressings are divided into a salad dressing having an oil content of at least 65%, for which an emulsifier other than an egg can be used, and a French dressing formed without using egg. Here, a problem resides in the use of the egg yolk as the emulsifier. It has been experimentally proved that the serum cholesterol level in the human body is increased by the intake of egg yolk. Therefore, the use of a large quantity of egg yolk to increase the quality of mayonnaise is not allowed. Nevertheless, if the derivative of formula (I) or the extract composed mainly of such a derivative is added to edible oil used for mayonnaise, it becomes possible to prevent an increase of the cholesterol level after the intake of mayonnaise, and it also becomes possible to increase the amount of egg yolk used for mayonnaise, and thus increase the quality of the mayonnaise. Furthermore, the quality of a salad dressing prepared by using egg yolk as the emulsifier can be improved by incorporating the derivative of formula (I) or extract composed mainly of such a derivative.

The effect of the derivative of formula (I) or the extract composed mainly of such a derivative as the functional factor can be increased by a combined use thereof with other substances, and the combined use of a fatty acid having 16 to 20 carbon atoms and 1 to 3 double bonds in the carbon chain, especially γ -linolenic acid (6,9,12-

octadecatrienoic acid) or dihomog γ -linolenic acid (8,11,14-eicosatrienoic acid), is preferred. In this case, the acid can be used directly or in the form of a salt of sodium, potassium or ammonium or an ester such as a methyl ester or an ethyl ester. Moreover, oils and fats containing these fatty acids can be used.

The cholesterol level-reducing and neutral fat level-reducing actions of the derivative of formula (I), the extract composed mainly of such a derivative, and the food containing the derivative or extract have been explained. As described in Japanese Patent Application No. 1-052950, the derivative of formula (I) or the extract composed mainly of the such a derivative can be an inhibitor for specifically inhibiting a Δ^5 -desaturase for converting dihomog γ -linolenic acid to arachidonic acid. It is expected that various pharmacological effects will be obtained by an increase of the eicosanoids of dihomog γ -linolenic acid brought about by an increase of the content of dihomog γ -linolenic acid. For example, an anti-inflammatory action, an anti-thrombosis action, and a hypotensive action can be expected, and the derivative of formula (I) and the extract composed mainly of such a derivative can be used as a remedy for related diseases, such as inflammatory diseases, heartvascular and thrombotic diseases, mental diseases, chest and prostate diseases, diabetes, endometritis, malnutrition, menstrual disorders, and malignant tumors. Accordingly, as the function attained by the present invention, there can be mentioned the anti-thrombosis action, the anti-inflammatory action, and the hypotensive action. Furthermore, these actions can be significantly enhanced by the effect derived from prostaglandin I by the combined use with γ -linolenic acid and dihomog γ -linolenic acid.

The derivative of formula (I) has a very high activity; this is made obvious from the fact that, even if sesamin was continuously administered (oral administration) to 7-weeks-old ICR male mice
5 at a dosage of 2.14 g/day/kg continuously for two weeks, no abnormal symptoms were observed.

The present invention will now be described in detail with reference to the following examples.

10 EXAMPLE 1

To 16.5 kg of sesame oil was added 94.5 l of hot methanol (60°C), the mixture was violently stirred to effect extraction, and then allowed to stand at room temperature overnight. The organic
15 solvent was removed from the upper methanol layer by distillation using a rotary evaporator, to obtain 424 g of an extract composed mainly of a derivative of formula (I). Then the extract was dissolved in 3.2 l of acetone, the solution was allowed to stand
20 at -80°C overnight, and the organic solvent was removed by distillation from the filtrate obtained by the filtration to obtain 103 g of an extract composed mainly of the derivative of formula (I). When the extract thus obtained was analyzed, it was
25 found that the extract contained 19.6% of sesamin, 30.6% of episesamin and 10.2% of sesaminol and episesaminol based on the extract, and the total content of these derivatives in the extract was 60.4%.

30 Eight-week-old male mice (CD-1 mice supplied by Nippon Charles River) were raised for one week with an ordinary feed (CE-2 feed supplied by Nippon Clea). The mice were then divided into 4 groups, each consisting of 10 mice, and the mice of
35 one group were raised with the same ordinary feed, and the mice of the other three groups were raised with a high cholesterol feed having 1% of chole-

terol, 0.2% of cholic acid and 5% of olive oil incorporated therein. Of the three groups to which the high-cholesterol feed was given, the two groups were raised with a feed obtained by incorporating
5 0.4 or 0.6% of the above-mentioned extract into the high-cholesterol feed. After two weeks' growth, the mice were fasted for 15 hours and blood was collected. The GOT and GPT activities in the serum were analyzed by an automatic biochemical analysis
10 apparatus (Model 7050 supplied by Hitachi). The results are shown in Table 1, and as seen from these results, increases of GOT and GPT were controlled by using a derivative of formula (I).

TABLE 1

	Ordinary feed	High- cholesterol feed	High- cholesterol feed + 0.4% of sesame oil extract	High- cholesterol feed + 0.6% of sesame oil extract
GOT (IU/L)	72 ± 24.6	161 ± 48.8	136 ± 53.7	104 ± 26.1
GPT (IU/L)	24 ± 5.5	151 ± 66.7	68 ± 18.7	82 ± 39.1

EXAMPLE 2

In the same manner as described in Example 1, mice were raised for one week with the ordinary feed, and the mice were divided into four groups, each consisting of 10 mice. The mice of one group were raised with the same ordinary feed, and the mice of the remaining three groups were raised with a high-cholesterol feed formed by adding 1% of cholesterol, 0.2% of cholic acid and 5% of evening primrose oil to the ordinary feed. A feed formed by adding 0.4 to 0.6% of a purified mixture comprising 61.5% of sesamin and 38.0% of episesamin to the high-cholesterol feed was given to the mice of the two groups among the three groups to which the high-cholesterol feed was given. After two weeks' growth, the mice were fasted for 15 hours and blood was collected. The GOT and GPT activities in the serum were measured, and the results are shown in Table 2. As seen from these results, the increase of GOT by the high-cholesterol feed was controlled by using the mixture of sesamin and episamin.

TABLE 2

	Ordinary feed	High- cholesterol feed	High- cholesterol feed + 0.4% of sesamin	High- cholesterol feed + 0.6% of sesamin
GOT (IU/L)	105 ± 31.8	141 ± 35.8	112 ± 35.6	87 ± 13.2
GPT (IU/L)	29 ± 5.1	58 ± 14.2	64 ± 23.1	45 ± 16.2

EXAMPLE 3

Eight-week-old male rats of the SD line (supplied by Nippon Clea) were raised for 1 week with an ordinary feed, and the rats were divided into 4 groups, each consisting of 6 rats. The rats of one group were raised with the same ordinary feed, and the rats of the remaining three groups were raised with a high-cholesterol feed comprising 20% of casein, 10% of beef tallow, 59.9% of granulated sugar, 4.0% of a mineral mixture, 0.85% of a vitamin mixture, 4.0% of a filter paper powder, 1.0% of cholesterol and 0.25% of bile acid. A feed formed by adding 1.0 or 2.0% of the mixture of sesamin and episesamin used in Example 2 to the above-mentioned high-cholesterol feed was given to the rats of two groups among the three groups to which the high-cholesterol feed was given. After 1 week's growth, blood was partially collected, and after two weeks' growth, blood was wholly collected. Each blood collection was effected after 17 hours' fasting. The GOT and GPT activities in the serum were measured. The results are shown in Table 3, and from these results, it is seen that the increase of GOT by the high-cholesterol feed was controlled by using the mixture of sesamin and episesamin.

TABLE 3

After 1 week's raising

	Ordinary feed	High- cholesterol feed	High- cholesterol feed + 1.0% of sesamin	High- cholesterol feed + 2.0% of sesamin
GOT (IU/L)	119 ± 37.8	140 ± 48.2	76 ± 12.8	63 ± 11.5
GPT (IU/L)	39 ± 9.9	23 ± 1.7	24 ± 3.4	26 ± 1.9

After 2 weeks' raising

	Ordinary feed	High- cholesterol feed	High- cholesterol feed + 1.0% of sesamin	High- cholesterol feed + 2.0% of sesamin
GOT (IU/L)	83 ± 11.5	102 ± 37.8	81 ± 21.5	76 ± 12.1
GPT (IU/L)	26 ± 4.3	21 ± 1.3	22 ± 2.3	27 ± 6.4

EXAMPLE 4

Nine-week-old male CDF-1 mice (supplied by Nippon Clea) were raised for 1 week, and the mice were divided into three groups, each consisting of 7 mice. The mice of two groups other than the control group were raised in a chamber filled with air containing 12 ppm of ethanol. After 1 week's growth, the mice were fasted for 16 hours, and blood was collected. The total cholesterol (T-CHO) content, the triglyceride (TG) content, the GOT and GPT activities and the total bilirubin content in the serum were measured, and the results are shown in Table 4.

The increase of the triglyceride content, the total bilirubin content, GOT, and GPT by the administration of the alcohol was significantly reduced. When the general motion of the mice was observed, it was seen that in the ordinary feed-given group, 5 mice of the seven mice were dragged out, but in the sesamin-containing feed-given groups, the motion was not different from the ordinary motion. Thus, a conspicuous difference was found.

TABLE 4

	Feed intake amount (g/mouse /day)	Sesamin intake amount (mg/mouse /day)	Serum total serum CHOL (mg/dl)	Serum TG (mg/dl)	Serum total BIL (mg/dl)	Serum GOT (IU/L)	Serum GPT (IU/L)
Ordinary feed	3.55	0	91.6±8.8	58.6±12.1	0.47±0.15	149.7±76.3	26.1±7.8
Ordinary feed + ethanol	2.45	0	100.9±10.2	237.3±124.2 ⁺⁺	1.61±1.32 ⁺	312.4±203.8 ⁺	39.6±31.9
Ordinary feed + ethanol + 1% of sesamin	2.43	24.3	89.4±8.5	83.0±19.0 ⁺ *	0.41±0.04	81.6±15.4 ⁺ **	18.3±1.6*

Note

CHOL:	Cholesterol
TG:	triglyceride
BIL:	bilirubin

to ordinary feed:	+ P < 0.05	to ordinary feed + ethanol: *	P < 0.05
++	P < 0.01	**	P < 0.01

EXAMPLE 5

Eight-week-old male CDF-1 mice (supplied by Nippon Clea) were raised for 1 week and were divided into three groups, each consisting of 7 mice. To two groups other than the control group, 1 mg/kg of carbon tetrachloride was administered in the abdominal cavity. To one of these two groups, simultaneously, 100 mg/kg of sesamin was forcibly orally administered. Then the mice were fasted for 16 hours and blood was collected. The total cholesterol (T-CHO), the triglyceride (TG) content, GOT, GPT and the total bilirubin content in the serum were measured. The results are shown in Table 5.

TABLE 5
Evaluation of Resistance to Acute Loading of Carbon Tetrachloride

	T-CHO (MG/DL)	TG (MG/DL)	GOT (IU/L)	GPT (IU/L)	ALP (IU/L)	T-BIL (MG/DL)
Control	105.00 ± 6.19	76.00 ± 8.27	122.9 ± 48.6	22.1 ± 4.9	227.40 ± 18.48	0.40 ± 0.13
Carbon tetra- chlor- ide	63.30 ± 6.92	48.90 ± 11.6	26468.0 ± 2071.6	28152.0 ± 1315.4	455.90 ± 45.37	2.90 ± 0.24
Carbon tetra- chlor- ide + sesamin	84.00 ± 11.99**	59.70 ± 5.50*	25274.0 ± 2398.0	31750.0 ± 3731.2	500.90 ± 36.51	1.30 ± 0.42***

Note * p < 0.05 vs. CCl4
 ** p < 0.01 vs. CCl4
 *** p < 0.001 vs. CCl4

EXAMPLE 6

Male rats of the Wister line were divided into two groups (control group and sesamin group), each consisting of 6 rats. The rats of the control group were raised for 22 days with a basic feed and the rats of the sesamin group were raised for 22 days with a feed formed by adding 0.5% of sesamin to the basic feed. The rats were fasted overnight, and 1 g/kg of ethanol (20%) was forcibly orally administered. After 1 and 3 hours, blood was collected from the tail vein and the alcohol concentration in blood was measured. After 1 hour from the point of the administration, the ethanol concentration was 0.5 mg/ml in the control group but the ethanol concentration was 0.27 mg/ml in the sesamin group. After 3 hours from the point of the administration, the ethanol concentration was 0.12 mg/ml in the control group but the ethanol concentration was 0.02 mg/ml in the sesamin group. Accordingly, it was confirmed that ethanol disappeared more quickly in the sesamin group than in the control group.

EXAMPLE 7

Examples of formulations containing a derivative of formula (I) will now be described, though the present invention is not limited by these formulation examples.

Formulation 1

With 20.5 g of silicic anhydride was mixed 0.5 g of a derivative of formula (I) and 79 g of corn starch was added to the mixture. Then, 100 ml of a 10% solution of hydroxypropyl cellulose in ethanol was added to the mixture, and according to customary procedures, the mixture was kneaded, extruded and dried to obtain a granule.

Formulation 2

With 20 g of silicic anhydride was mixed 7 g of a derivative of formula (I) and 10 g of microcrystalline cellulose, 3.0 g of magnesium

stearate and 60 g of lactose were added to the mixture. The mixture was formed into tablets having a diameter of 7 mm and weight of 100 mg by using a single-shot tableting machine.

5 Formulation 3

In 200 g of a nonionic surface active agent (TO-10M supplied by Nikko Chemicals) was dissolved 2.5 g of a derivative of formula (I) under heating at 122°C. Then, 4.8985 g of a sterilized
10 physiological saline solution was added to the solution and the mixture was thoroughly stirred. The liquid was sterilely distributed into vials, and the vials were sealed to obtain injections.

EXAMPLE 8

15 In 180 ml of salad oil was dissolved 0.9 g of the extract composed mainly of derivatives of formula (I), which was obtained in Example 1. Separately, a vessel was charged with one egg yolk, 3 g of table salt, 1 g of mustard, sugar, a spice
20 and a chemical seasoning, and 3 ml of vinegar was added into the vessel and the mixture was strongly stirred by a whip to form a mayonnaise base. Then, 12 ml of vinegar and 180 ml of the salad oil containing the derivatives of formula (I) dissolved
25 therein were added to the mayonnaise base with stirring to obtain a mayonnaise containing the derivatives of formula (I).

EXAMPLE 9

To 100 g of a butter milk-free butter fat
30 obtained at the stirring operation (churning) in the butter-preparing process, 2 g of the extract composed mainly of derivatives of formula (I), which was obtained in Example 1 of the present invention, was added, and the mixture was subjected to the
35 kneading operation (working) to obtain a butter containing the derivatives of formula (I), which had a homogeneous texture.

EXAMPLE 10

The mayonnaise containing the derivatives of formula (I), which was obtained in Example 8, and the butter containing the derivatives of formula (I), which was obtained in Example 9, were compared with the mayonnaise and butter prepared without adding a derivative of formula (I) and the differences of the taste and flavor were evaluated by five experts. As a result, it was confirmed that the inherent quality was not influenced by the addition of a derivative of formula (I).

EXAMPLE 11

Four-week-old male rats of the SD line were raised for 3 weeks with a feed containing 10% of the butter containing the derivative of formula (I) which was obtained in Example 9 (derivative-added group), or a butter not containing a derivative of formula (I) (derivative-free group). After 3 weeks, the body weight, the liver weight, the plasma cholesterol content, the plasma triglyceride content and the plasma phospholipid content were measured. The results are shown in Table 6.

As apparent from the results shown in Table 6, even if the food containing the derivative of formula (I) was given, there was no difference of the increase of the body weight of the liver weight during 3 weeks' raising and the growth was not influenced at all. Furthermore, the cholesterol and triglyceride levels in the plasma were reduced by giving the food containing the derivative of formula (I).

TABLE 6

	Derivative-added group	Derivative-free group
Initial body weight (g)	102 $\pm$ 3	103 $\pm$ 3
Final Body weight (g)	272 $\pm$ 13	275 $\pm$ 11
Body weight increase (g)	170 $\pm$ 11	172 $\pm$ 10
Body weight increased per day (g/day)	8 $\pm$ 0	8 $\pm$ 0
Total intake (g)	388 $\pm$ 9	384 $\pm$ 13
Intake per day (g/day)	18 $\pm$ 1	18 $\pm$ 1
Feed efficiency	0.43 $\pm$ 0.01	0.43 $\pm$ 0.01
Liver weight (g)	15.23 $\pm$ 0.52	14.87 $\pm$ 0.67
Plasma cholesterol level (mg/dl)	76.2 $\pm$ 4.3	112.7 $\pm$ 4.9
Plasma triglyceride level (mg/dl)	145.7 $\pm$ 21.5	214.3 $\pm$ 11.4
Plasma phospholipid level (mg/dl)	211.4 $\pm$ 7.6	251.8 $\pm$ 17.9

EXAMPLE 12

From the extract composed mainly of a derivative of formula (I) which was obtained in Example 1, Δ^5 -desaturase inhibitors, i.e., sesamin, episesamin, sesaminol and episesaminol, were obtained according to the method described in Japanese Patent Application No. 1-052950. Sesamin-containing mayonnaise and sesamin-containing butter were prepared in the same manner as described in Examples 7 and 8 by using 0.54 g and 1.2 g of sesamin, respectively. Similarly, foods containing the derivatives of formula (I) singly or in combination were obtained. The derivative of formula (I) was a colorless (white) crystal and had no taste or smell. Accordingly, the derivative of formula (I) did not have any influence on the inherent quality of the foods.

EXAMPLE 13

To 20 ml of water was added 2 g of β -cyclodextrin, and 0.2 g of sesamin dissolved in a small amount of acetone was added to the mixture under agitation by a stirrer. The mixture was stirred at room temperature for 4 hours and freeze-dried to obtain 2.2 g of a cyclodextrin inclusion compound containing 10% of sesamin. A sesamin-containing juice was prepared by adding 1 g of the obtained powder to 100 ml of a juice.

EXAMPLE 14

The procedures of Example 13 were repeated by using a derivative of formula (I) and the extract composed mainly of such a derivative. Juices containing the derivative of formula (I) and the extract, respectively, were obtained.

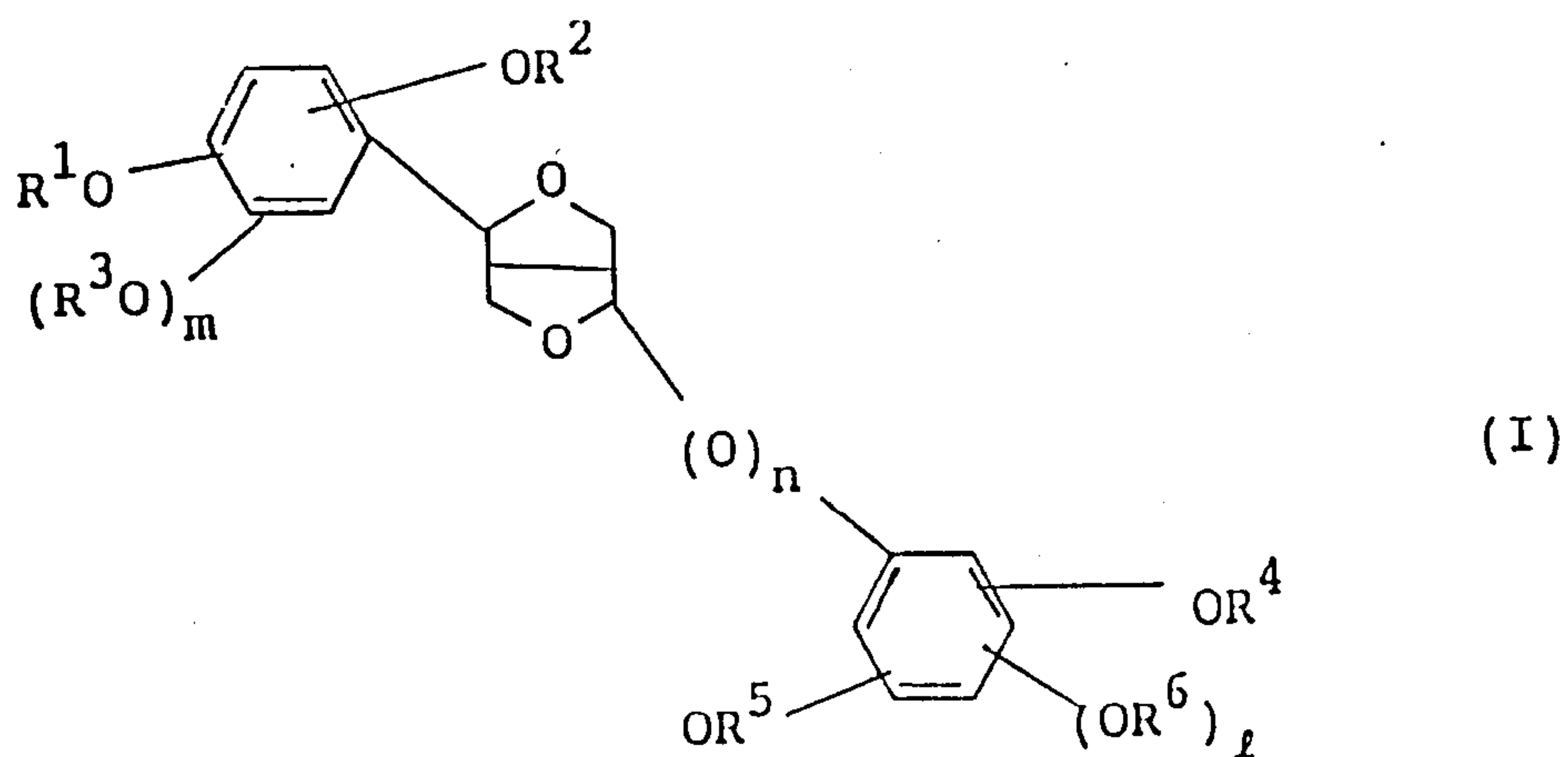
EXAMPLE 15

In 82 g of a starting oil and fat material comprising 30% of edible hardened soybean oil, 10% of edible hardened cotton seed oil, 40% of soybean

salad oil, 10% of palm oil and 10% of corn oil, 1 g of sesamin was incorporated and dissolved. Then, 15 g of water, 1.2 g of table salt, 0.3 g of monoglyceride, 0.1 g of lecithin, a trace of carotene, 0.00001 g of a flavor and 1.4 g of a milk solid were added to the solution, and the mixture was emulsified, rapidly cooled, and kneaded to obtain a sesamin-containing margarine.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A cholesterol or neutral fat level reducer comprising, as active ingredient, a dioxabicyclo-[3.3.0]octane derivative having the general formula (I):



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 independently represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or R^1 and R^2 and/or R^4 and R^5 together form a methylene group or an ethylene group, and n , m and l are 0 or 1.

2. A cholesterol or neutral fat level reducer according to claim 1, wherein the dioxabicyclo-[3.3.0]octane derivative is selected from the group consisting of sesamin, sesaminol, episesamin, episesaminol, sesamolin, 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane, 2,6-bis-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane and 2-(3,4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenoxy)-3,7-dioxabicyclo[3.3.0]octane.