Effect of combination of edible oils on blood pressure, lipid profile, lipid peroxidative markers, antioxidant status, and electrolytes in patients with hypertension on nifedipine treatment

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ABSTRACT

الأهداف: التحقق من تأثير الزيوت القابلة للأكل والمكونة من خليط زيت دوار الشمس والسمسم وذلك على كل من: ضغط الدم، ومقاييس الجسم الأنثروبومترية، ودهون الجسم، والمؤشرات الناتجة عن تفاعل بيروكسيداز الشحوم، وحالة التأكسد، والتكهرل لدى المرضى المصابين بارتفاع ضغط الدم والذين يأخذون عقار النيفيديبين.

الطريقة: لقد تم تقسيم المرضى في هذه الدراسة إلى 4 مجموعات وهي كالتالي: المجموعة الطبيعية (العدد=14)، ومجموعة المرضى المصابين بارتفاع ضغط الدم (العدد=38)، ومجوعة التحكم التي تأخذ عقار النيفديبين (العدد=12)، والمجموعة التي تأخذ عقار النيفيديبين مع خليط زيوت دوار الشمس والسمسم (العدد=26). تم إعطاء خليط زيت دوار الشمس والسمسم للمرضى، وقد كان المصدر الوحيد للدهون وذلك لمدة تصل إلى 45 يوماً. أجريت مقاييس الجسم الأنثروبومترية وضغط الدم في بداية الدراسة وبعد انقضاء 45 يوماً. لقد تم أيضاً قياس كلاً من: المؤشرات الناتجة عن تفاعل بيروكسيداز الشحوم، ومضادات الأكسدة الأنزيمية وغير الإنزيمية، واختبارات تحليل الدهون والتكهرل في الدم.

النتائج: أشارت نتائج الدراسة إلى أن استهلاك خليط زيت السمسم ودوار الشمس مع أخذ عقار النيفيديبين أدى إلى حدوث انخفاض واضح في مستويات كلاً من: ضغط الدم، والمؤشرات الناتجة عن تفاعل بيروكسيداز الشحوم، ودهون الجسم الغير حميدة، وكلوريد الصوديوم، ولكنها بالمقابل أدت إلى زيادة مستويات الكولسترول الدهني عالي الكثافة، ومضادات الأكسدة الأنزيمية وغير الإنزيمية، والبوتاسيوم وذلك عند مقارنة مجوعة التحكم التي تأخذ عقار النيفديبين وحده بالمجموعة التي تأخذ عقار النيفيديبين مع خليط زيت دوار الشمس والسمسم.

خاتمة: أثبتت الدراسة فعالية الجمع بين النيفيديبين وخليط زيت دوار الشمس والسمسم في الحماية من ارتفاع ضغط الدم وتفاعل بيروكسيداز الشحوم، بالإضافة إلى زيادة استقرار مستويات مضادات الأكسدة الأنزيمية وغير الإنزيمية، ودهون الجسم، والتكهرل وذلك لدى المرضى المصابين بارتفاع ضغط الدم.

Objectives: To determine the effect of combination of edible oils on blood pressure, anthropometric parameters, lipid profile, lipid peroxidative markers, antioxidant status and electrolytes in drug (nifedipine) taking patients with hypertension.

Methods: In this study, patients were separated into 4 groups. Normal (n=14), hypertensive patients (n=38), 38 patients under medication with nifedipine were divided into 2 groups nifedipine control (n=12) and nifedipine + oil combination (sesame + sunflower oil) groups (n=26). Sesame and sunflower oil combination was supplied to patients and instructed to use it as the only oil source for 45 days. Blood pressure and anthropometric parameters were measured at baseline and after 45 days. Lipid peroxidative markers, enzymatic and non-enzymatic antioxidants, lipid profile and electrolytes in blood were also measured. The study took place at Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalainagar, India between January 2005 and December 2008.

Results: Nifedipine and oil-mix consumed patients significantly decreased the blood pressure, lipid peroxidative markers, lipid profile excluding the high density lipoprotein cholesterol (HDL-C), sodium, chloride, and increased enzymatic, non-enzymatic antioxidants, HDL-C and potassium levels when compared to nifedipine alone treated hypertensive patients.

Conclusion: Nifedipine and oil-mix provided good protection over blood pressure and lipid peroxidation, and brought enzymatic and non-enzymatic antioxidants, lipid profile, and electrolytes towards normalcy in hypertensive patients.

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Hypertension is the most common cause of cardiovascular and cerebrovascular complications.[1] It is a major risk factor for stroke, myocardial infarction, heart failure, chronic kidney disease, progressive atherosclerosis, and dementia.[2] The role of oxidative stress in the pathogenesis of hypertension has been advanced in recent years.[3-4] It has been reported that hypertension may, in part, develop as a result of increased reactive oxygen species.[5] Natural antioxidants and polyunsaturated fatty acids show protective function against hypertension.[6] Frenoux et al[7] previously reported that polyunsaturated fatty acid rich diet improves antioxidant status in rats. The development of hypertension and cardiovascular hypertrophy were markedly attenuated in animals by fed with sesamin containing diets. Sesame seeds and oil have long been categorized as traditional health food in India and other East Asian countries. Sesame oil contains considerable amounts of the sesame lignans: sesamin, episesamin, and sesamolin, Vitamin E, polyunsaturated fatty acid, monounsaturated fatty acid. Dietary sesamin ameliorated the development of hypertension and cardiac hypertrophy in renal hypertensive rats. Sunflower oil contains 65% polyunsaturated fatty acids (PUFA), 23% monounsaturated fatty acids (MUFA) and 70 mg/100 g of vitamin E. Lignans present in sesame oil are thought to be responsible for many of its unique chemical and physiological properties, including its antioxidant and antihypertensive properties.[8-11]

Sankar et al[12] reported that sesame oil reduces the blood pressure (BP), lipid profiles (total cholesterol, triglycerides, very low density lipoprotein-C, low density lipoprotein-C, total cholesterol: HDL ratio and increased high density lipoprotein-C levels) and lipid peroxidation by increasing enzymatic and nonenzymatic antioxidants. In this study, we investigated the effect of equal combination of sesame and sunflower oils on BP, lipid profile, oxidative status, and electrolyte levels in nifedipine-taking patients with hypertension.

Methods. Male patients were selected for the study and separated into 4 groups: Normal (n=14), hypertensive patients (n=38); 38 patients under medication with nifedipine were divided into 2 groups nifedipine control (n=12) and nifedipine + oil combination (sesame + sunflower oil) groups (n=26). Thirty-eight patients with mild to moderate hypertension, who were on treatment with nifedipine (20-30 mg/dL), a calcium channel blocker, as an antihypertensive medication, aged from 45-55 years were recruited from the Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalainagar, India between January 2005 and December 2008. The study was approved by the Institutional Human Ethical Committee of Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalainagar, India. Written consent was obtained from each participant after explaining the nature and objective of the study; and a questionnaire was completed with regard to the family history and life style of the patient.

The criteria for inclusion in the patient group was established-hypertension, defined either by the need for chronic antihypertensive treatment or in untreated subjects by a systolic blood pressure (SBP) greater than 140 mm Hg or a diastolic blood pressure (DBP) greater than 90 mm Hg or both. Subjects with clinical or biological signs of secondary hypertensions were excluded; pregnant female, lactating mothers, chronic alcoholics and patients with diabetic hypertension were also excluded. They had no other disease.

Drug taking-hypertensive patients were consuming oil-mix for 45 days. Sesame (VVS, Idhayam Company, Virudhunagar, Tamilnadu, India) and sunflower oils (SVS Oil Mills, Thiruvotriyur, Chennai, India) (1:1) were purchased from local market. In a family, with 4 members, 4 kg of oil mix was given per month approximately 35 g/day/person. The patients were instructed to use the oil mix as sole edible oil for cooking, salad preparation, and so forth. The BP, lipid profile, lipid peroxidative markers, antioxidant status and electrolyte levels was measured at baseline and after 45 days.

Blood pressure was measured by the same physician between 9 a.m. and 10 a.m. using the standard mercury sphygmomanometer (Erkameter 3000, Wall Model; Ricahrd Kallmeyer, Nachforschung, Badtolz, Germany). Patients and subjects were at rest for 10 minutes before the blood pressure measurement, without talking, with the legs uncrossed and with the arm supported at heart level. Measurements were repeated 3 times and the average of the lowest 2 values was used in the analysis. Systolic blood pressure was recorded at the first appearance (Phase I) and diastolic blood pressure at the disappearance (Phase V) of Korotkoff's sound.

Blood samples were collected in heparinized tubes at the beginning and end, after an overnight fasting by venipuncture. Plasma was separated by centrifuging at 3000 rpm for 15 minutes and stored at 4°C until analysis.After plasma separation, the buffy coat was removed and the packed cells were washed 3 times with physiological saline. A known volume of erythrocytes was lysed with hypotonic phosphate buffer, pH 7.4.

Total cholesterol (TC),[13] high density lipoprotein cholesterol (HDL-C),[14] and triacylglycerol (TG),[15] concentrations in the plasma were determined by standard enzymic methods with a semi-autoanalyser (Bayer RA150, Germany) using commercially available kits. Low density lipoprotein cholesterol (LDL-C) was

calculated using Friedwald equation.[16] Thiobarbituric acid reactive substances (TBARS),[17] and conjugated dienes (CD):[18] enzymatic antioxidants, such as superoxide dismutase (SOD),[19] catalase (CAT),[20] glutathione peroxidase (GPx),[21] non-enzymatic antioxidants such as GSH,[22] vitamin E,[23] vitamin C[24] and ß-carotene.[25] Plasma electrolytes such us sodium,[26] potassium, and chloride[27] were also estimated.

Statistical analyses were carried out using the Statistical Package for Social Sciences Version 12 (SPSS Inc., Chicago, IL). One way analysis of variance and Duncan's multiple range test (DMRT) for comparing the group means. A p value <0.05 was considered statistically significant.

Results. Table 1 shows the effect of sesame and sunflower (1:1) oil-mix on blood pressure and anthrophometric parameters in nifedipine-taking patients with hypertension. Treatment with sesame and sunflower oil-mix on BP (systolic blood pressure, diastolic BP, and anthrophometric parameters such as weight (kg) and body mass index (kg/m^2) were improved towards normalcy when compared to nifedipine alone treated subjects.

Table 2 shows the effect of sesame and sunflower (1:1) oil-mix on lipid profile in nifedipine-taking patients with hypertension. Treatment with sesame and sunflower oil-mix on total cholesterol, triglycerides, very low density lipoprotein cholesterol, low density lipoprotein cholesterol were decreased and high density lipoprotein cholesterol were increased when compared to nifedipine alone treated subjects.

Table 3 shows the effect of sesame and sunflower (1:1) oil-mix on lipid peroxidative markers and electrolytes in nifedipine-taking patients with hypertension. Treatment with sesame and sunflower oil-mix on

Table 1 - Effect of nifedipine-oil-mix on blood pressure and anthropometric parameters in patients with hypertension.

Parameters	Normal (n=14)	Baseline (n=38) (0th day)	Nifedipine control (n=12) (45th day)	Nifedipine + sesame + sunflower oil (n=26) (45th day)
Systolic blood pressure (mm Hg)	125.19 ± 8.82^a	163.97 ± 11.86^d	146.86 ± 9.73^c	132.78 ± 8.80^b
Diastolic blood pressure (mm Hg)	83.19 ± 6.21^a	103.39 ± 7.59^c	95.59 ± 6.52^b	84.16 ± 6.30^a
Age (years)	49.23 ± 3.60^a	53.18 ± 4.02^a	50.08 ± 3.74^a	51.32 ± 3.05^{a,*}
Weight (kg)	59.10 ± 4.54^a	71.04 ± 5.17^d	67.17 ± 4.88^c	62.91 ± 4.52^b
Body mass index (kg/m^2)	22.78 ± 1.40^a	26.80 ± 1.59^c	25.57 ± 1.54^b	23.78 ± 1.41^b

Values are means ± standard deviation for each group. *one reply.
^{a,b,c,d} Values in a column followed by different superscript letters differ significantly (p<0.05) (Duncan's multiple range test).

Table 2 - Effect of nifedipine-oil-mix on lipid profile in patients with hypertension.

Parameters	Normal (n=14)	Baseline (n=38) (0th day)	Nifedipine control (n=12) (45th day)	Nifedipine + sesame + sunflower oil (n=26) (45th day)
Total cholesterol (TC)(mg/dL)	169.25 ± 11.92^a	234.35 ± 16.51^c	228.80 ± 16.14^c	180.25 ± 12.10^b
Triglycerides (mg/dL)	109.49 ± 8.01^a	167.04 ± 11.37^c	161.96 ± 11.35^c	128.65 ± 8.96^b
High density lipoprotein-C (mg/dL)	46.35 ± 3.24^c	39.28 ± 2.90^a	40.09 ± 2.98^a	44.10 ± 3.28^b
Very low density lipoprotein-C(mg/dL)	21.04 ± 1.56^a	33.11 ± 2.26^c	32.81 ± 2.30^c	25.05 ± 1.75^b
Low density lipoprotein-C (mg/dL)	101.20 ± 7.09^a	161.96 ± 11.86^c	155.36 ± 11.59^c	112.65 ± 8.55^b
TC/HDL-C	3.59 ± 0.25^a	6.07 ± 0.36^c	5.73 ± 0.325^c	4.00 ± 0.24^b

Values are means ± Standard deviation for each group.
^{a,b,c}Values in a column followed by different superscript letters differ significantly (p<0.05) (Duncan's multiple range test).

Table 3 - Effect of nifedipine-oil-mix on antioxidant status in patients with hypertension.

Parameters	Normal (n=14)	Baseline (n=38) (0th day)	Nifedipine control (n=12) (45th day)	Nifedipine + sesame + sunflower oil (n=26) (45th day)
Superoxide dismutase (U*/mg Hb)	3.60 ± 0.25^c	2.50 ± 0.17^a	2.61 ± 0.19^a	3.20 ± 0.23^b
Catalase (U$^\$$/mg Hb)	7.90 ± 0.57^c	6.11 ± 0.42^a	6.23 ± 0.43^a	7.34 ± 0.51^b
Glutathione peroxidase (U$^\#$/mg Hb)	8.09 ± 0.59^c	6.87 ± 0.48^a	6.92 ± 0.48^a	7.64 ± 0.56^b
Vitamin E (mg/dL)	1.36 ± 0.07^c	0.54 ± 0.03^a	0.55 ± 0.03^a	1.03 ± 0.06^b
Vitamin C (mg/dL)	1.29 ± 0.07^c	0.75 ± 0.04^a	0.78 ± 0.04^a	0.90 ± 0.05^b
Beta-carotene (mg/dL)	0.82 ± 0.04^c	0.42 ± 0.03^a	0.41 ± 0.02^a	0.70 ± 0.04^b
Reduced glutathione (mg/dL)	35.37 ± 2.47^c	23.83 ± 1.77^a	24.52 ± 1.71^a	30.10 ± 2.12^b

Values are means ± Standard deviation for each group. ^{a,b,c}Values in a column followed by different superscript letters differ significantly (p<0.05) (Duncan's multiple range test). U* = Enzyme concentration required for 50% inhibition of NBT reduction/minute. U$^\$$ = µmol of hydrogen peroxide consumed/minute, U$^\#$= µmol of GSH utilized/minute

Table 4 - Effect of nifedipine-oil-mix on lipid peroxidative markers and electrolytes in patients with hypertension.

Parameters	Normal (n=14)	Baseline (n=38) (0th day)	Nifedipine control (n=12) (45th day)	Nifedipine + sesame + sunflower oil (n=26) (45th day)
Thiobarbituric acid reactive substances (nmol/ml)	3.61 ± 0.18[a]	6.22 ± 0.40[c]	6.18 ± 0.42[c]	4.15 ± 0.29[b]
Conjugated dienes (nmol/mL)	0.82 ± 0.05[a]	1.80 ± 0.10[c]	1.78 ± 0.09[c]	1.11 ± 0.05[b]
Sodium (mEq/L)	136.27 ± 9.55[a]	144.83 ± 11.15[b]	142.90 ± 10.40[b]	130.05 ± 9.84[a]
Potassium (mEq/L)	4.59 ± 0.34[c]	3.80 ± 0.27[a]	3.90 ± 0.27[a]	4.22 ± 0.30[b]
Chloride (mEq/L)	101.34 ± 8.00[a]	112.19 ± 8.39[c]	109.04 ± 8.25[b,c]	105.23 ± 7.87[a,b]

Values are means ± Standard deviation for each group.
[a,b,c]Values in a column followed by different superscript letters differ significantly (p<0.05) (Duncan's multiple range test).

superoxide dismutase, catalase, glutathione peroxidase, and Vitamin E, Vitamin C, Beta-carotene and reduced glutahione were improved when compared to nifedipine alone treated subjects.

Table 4 shows the effect of sesame and sunflower (1:1) oil-mix on antioxidant status in nifedipine-taking patients with hypertension. Treatment with sesame and sunflower oil-mix on thiobarbituric acid reactive substances, conjugated dienes, sodium, potassium and chloride were maintaining the levels when compared to nifedipine alone treated subjects.

Discussion. In patients with hypertension the BP level was at stage 2 and on treatment with nifedipine the BP reached at stage 1. Nifedipine, a calcium channel blocker, inhibits the influx of calcium ions into the cell, leading to the relaxation of vascular smooth muscle and thus lowering blood pressure. Nifedipine and oil-mix have brought blood pressure to prehypertension stage, which may be due to the combined effect of sesamin, polyunsaturated fatty acids and vitamin E, apart from nifedipine. Several studies reported the antihypertensive effect of sesamin, a lignan from sesame oil, in experimental hypertensive models.[28] Sesamin containing diets when fed to the animals, the development of hypertension and cardiovascular hypertrophy were markedly attenuated. Sesamin has Calcium (Ca2+) antagonistic activity that may be additive with nifedipine by further lowering blood pressure.[10] In the present study, body weight and BMI increased in patients with hypertension. Consumption of nifedipine as well as nifedipine and oil-mix decreased body weight and BMI in patients with hypertension. Nifedipine and oil-mix showed a better and a significant reduction than nifedipine alone and further reduced BMI to normal level.

Previously, numerous studies reported that, oils containing saturated fatty acids increased the serum TC, TG and, in particular, LDL-C levels, while those enriched in unsaturated fatty acids decreased the level of TC, TG, and LDL-C.[29] The reduction of these parameters could be due to the presence of polyunsaturated fatty acids in the sesame and sunflower oil. Prior reports show that sesame lignans such as sesamin and episesamin modulate cholesterol metabolism by inhibiting the synthesis and absorption of cholesterol in the stroke-prone spontaneously hypertensive rats.[30] Substitution of sesame oil as edible oil lowered plasma triglyceride concentration.[31] Diets high in monounsaturated fatty acids have been found to be relatively hypocholesterolemic or hypotriacylglycerolemic, respectively, although in some cases it can effectively lower blood pressure.[32] A greater increase of LDL-C and VLDL-C may also cause a greater decrease of HDL-C as there is a reciprocal relation between the concentration of VLDL-C and HDL-C. After treatment, the levels of LDL-C and VLDL-C decreased, and HDL-C increased in nifedipine-oil-mix consumed patients.

Lipid peroxidation is one of the reactions induced by oxidative stress; it is especially active in those tissues having membranes rich in polyunsaturated fatty acids. A lot of oxygenated compounds, particularly aldehydes such as malondialdehyde and conjugated dienes, are produced during the attack of free radicals to membrane lipoproteins and polyunsaturated fatty acids.[33] We observed increased concentration of TBARS and conjugated dienes, indices of lipid peroxidation in the plasma of hypertensive patients. A marked decrease of lipid peroxidation was observed in nifedipine-oil-mix group only and not in nifedipine alone treated patients. This reduction may be due to the presence of lignans, in sesame oil such as sesamolin, sesamol and sesamolinol. Sesamolin is metabolized to sesamol and sesamolinol in vivo and that both of these compounds strongly inhibit lipid peroxidation. Thus, the metabolites of sesamolin may contribute to the antioxidative properties of sesame lignans and reduce susceptibility to some forms of oxidative stress.[34] Monounsaturated fatty acids from sunflower oil have been shown to protect LDL against oxidative damage. Vitamin E in sunflower oil enhances

the detoxification of hydroxyl and peroxyl radicals thereby controlling lipid peroxidation and also confers some early protection against peroxidation of LDL.[35] Free radical scavenging enzymes such as SOD, CAT and GPx are the first line of cellular defense against injury, involved in the disposal of superoxide anions and hydrogen peroxide. The antioxidant enzymes, SOD, and CAT are widely distributed in all cells and are present in high amounts in erythrocytes.[36]

In our study, we observed decreased activities of SOD, CAT and GPx in the erythrocytes of hypertensive patients due to increased utilization of the enzymes. Decreased activities of SOD and CAT will result in the accumulation of reactive free radicals leading to deleterious effects on cell membrane integrity and membrane function. Decrease in SOD activity could be due to inactivation of the enzyme by cross-linking or due to exhaustion of the enzyme by increased peroxidation. Glutathione peroxidase is a selenium dependent enzyme catalyzing peroxide reduction utilizing GSH as the substrate and converting it to GSSG. We have observed a decrease in GPx activity in the erythrocyte of hypertensive patients. After treatment, elevation of enzymatic antioxidants such as SOD, CAT and GPx activities were observed only in nifedipine-oil-mix group and not in nifedipine alone treated patients. Ali et al[37] found that dietary sesamin was metabolized in the liver and converted to an antioxidative catechol form. This metabolite might exhibit direct radical scavenging activity in the vascular wall. Sesamin may reduce the vascular O_2 production by inhibiting the activity of an NADPH oxidase, an enzyme, which is known to be a main source of O_2 production in the vasculature.[38]

The non-enzymatic scavengers such as glutathione, ascorbic acid, α-tocopherol and beta-carotene are second line defense scavengers. The scavenging capacity of the human body depends mainly on the pool of GSH and SH groups. We observed a decreased plasma GSH level in hypertensive patients, which may be due to an increased utilization of GSH. Ascorbic acid is the main water-soluble chain breaking antioxidant that reacts with oxygen free radicals. It provides protection to plasma lipids and lipid membrane. In our study, we observed a significant decrease in the level of vitamin C, which could be due to increased utilization as an antioxidant defense against increased ROS or could be due to decreased GSH level, because GSH is involved in recycling vitamin C.[39] Vitamin E is the most effective chain breaking lipid soluble antioxidant present in cell membrane and it plays a major role in maintaining cell membrane integrity by limiting lipid peroxidation by ROS. Intake of vitamin E is associated with a lower risk of coronary heart disease and also protects vascular dysfunction by reducing oxidative stress.[40] Reduction of vitamin E levels may be due to the increased utilization in scavenging the ROS or could be due to decreased vitamin C concentration because there is a well established synergism between vitamin E and vitamin C.[41] Beta-carotene is a unique chain breaking lipid soluble antioxidant, which traps the peroxyl radicals. It has also been reported to have a substantial singlet oxygen quenching ability and it also inhibits lipid peroxidation initiated by xanthine oxidase,[42] which produces superoxide anion during its oxidation of hypoxanthine to xanthine and xanthine to uric acid. We observed a decreased level of plasma beta-carotene in hypertensive patients, which could be due to increased utilization to trap the ROS. Low levels of antioxidants enzymes observed in this study, in untreated hypertensive patients may be due to the increased utilization of the enzymes. After treatment the levels of GSH, vitamin C, vitamin E and beta-carotene increased in nifedipine-oil-mix consumed patients, which may be due to antioxidant activities of sesame lignans and vitamin E in oils.

In this study, we observed increased sodium and chloride and decreased potassium levels in the plasma of hypertensive patients. Many investigators have reported positive association between blood pressure and sodium intake or urinary excretion[43,44] and in the population dietary sodium intake is low and blood pressure is low and diets are usually rich in potassium. Nifedipine-oil-mix consumed patients show decreased levels of Na+ and increased level of K+. Research has consistently demonstrated that increasing K+ significantly lowers BP among salt sensitive individuals who show increased blood pressure in response to high Na+ intake.[45] Limitation of this study, we did not give the oil mix to the normal patients.

In conclusion, our results indicate that combination of nifedipine-oil-mix offers better protection compared to nifedipine alone treated hypertensive patients. The treatment with oil-mix further possesses antihyperlipidemic and antioxidant properties besides normalizing the electrolytes in patients with hypertension. Hence, we propose that, the combination of sesame and sunflower oil mix reduces the risk of cardiovascular disease. We recommend that further studies of this combination of oil mix on different race and regions be evaluated.

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