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Synthesis and antioxidant, anti-inflammatory and gastroprotector activities of anethole and related compounds

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Abstract—Some derivatives of *trans*-anethole [1-methoxy-4-(1-propenyl)-benzene] (**1**) were synthesized, by introducing hydroxyl groups in the double bond of the propenyl moiety. Two types of reactions were performed: (i) oxymercuration/demercuration that formed two products, the mono-hydroxyl derivative, 1-hydroxy-1-(4-methoxyphenyl)-propane (**2**) and in lesser extent the dihydroxyl derivative, 1,2-dihydroxy-1-(4-methoxyphenyl)-propane (**3**) and (ii) epoxidation with *m*-chloroperbenzoic acid that also led to the formation of two products, the dihydroxyl derivative (**3**) and the correspondent *m*-chloro-benzoic acid mono-ester, 1-hydroxy-1(4-methoxyphenyl)-2-*m*-chlorobenzoyl-propane (**4**). The structures of these compounds were confirmed mainly by mass, IR, ^{1}H and ^{13}C NMR spectral data. The activity of anethole and hydroxylated derivatives was evaluated using antioxidant, anti-inflammatory and gastroprotector tests. Compounds (**2**) and (**3**) were more active antioxidant agents than (**1**) and (**4**). In the anti-inflammatory assay, anethole showed lower activity than hydroxylated derivatives. Anethole and in lesser extent its derivatives **2** and **4** showed significant gastroprotector activity. All tested compounds do not alter significantly the total number of white blood cells.

1. Introduction

Anethole [1-methoxy-4-(1-propenyl)-benzene] is largely used as a flavour agent in food industry, in cakes, ice-creams and alcoholic beverages and presents several pharmacological activities as oestrogenic action,[1] depressive action to the central nervous system,[2] psicoleptic properties,[3] insecticide,[4] anticarcinogenic,[5] anti-inflammatory[6] and anesthetics activity.[7] Anethole was suggested to liberate Ca^{2+} from sarcoplasmatic reticule in skeletal muscle.[8] This compound and analogous are antioxidants by inhibition of lipid peroxidation.[9–11] Trithione and diallyl disulfide derivatives inhibited colon adenocarcinoms.[5,12–15]

Studies of chemical compounds and their derivatives related with a specific pharmacological activity to find a quantitative structure–activity relationship is very useful for the rational planning of new drugs and have brought many benefits for developing new treatments. Anethole, due to its many pharmacological activities, was chosen as the lead compound to synthesize some derivatives via introduction of hydroxyl groups in the double bond of the lateral chain (Fig. 1) and determine their antioxidant, anti-inflammatory and gastroprotector properties.

2. Results and discussion

The antioxidant test used in this study evaluates the capacity of compounds to scavenger DPPH radical species. DPPH (1,1-diphenyl-2-picrylhydrazyl) is a stable radical that presents an absorption maximum at 515 nm. The generation of free radicals is associated with aging and innumerable pathological processes like cancer and neurodegenerative diseases.[16] On the DPPH assay all compounds were tested at the same concentration (10 mM). Compounds **2** and **3** showed superior action than anethole and compound **4** (Fig. 2). The standard antioxidants BHT and α-tocoferol presented

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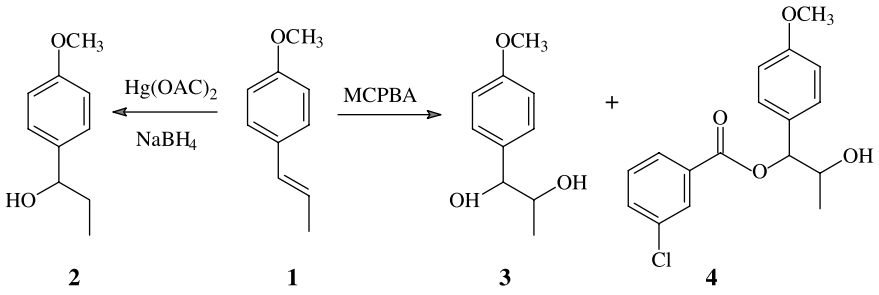

Figure 1. Reactional scheme of the synthesis of anethole derivatives.

stronger activity. Moreover, the introduction of hydroxyl groups in the double bond of the lateral chain of the anethole molecule, as in compounds **2** and **3**, increased the antioxidant activity. Phenolic compounds and alcohols with hydroxyl groups in allylic positions were the most active among many other compounds present in essential oils.[17] The majority of synthetic and natural antioxidant substances used in the industry contains phenolic groups.[18]

Anethole did not display significant anti-inflammatory activity in the evaluated model of vascular permeability assay. However, its derivatives presented higher activity (Table 1)—when compared with the control (animals that receive only saline). All hydroxylated derivatives (30 mg/kg) were as active as the reference drug indometacin (10 mg/kg) at $P < 0.001$, and for compound **2**, using 300 mg/kg, the differences are significantly higher than the reference drug ($P < 0.05$). These results suggest that the anti-inflammatory activity of anethole can be activated with modifications in the conjugated double bond of its propenyl moiety with introduction of hydroxyl groups. The metabolism of the anethole mainly occurs in the liver by oxidation and epoxydation reactions to form polar compounds among them the compounds **2** and **3**.[19] Therefore the anti-inflammatory data of this report suggests that the anti-carcinogenic action[5] and anti-inflammatory properties of anethole[6] may be related with its metabolites. These results point out the existence of a correlation between the antioxidant and the anti-inflammatory activity of the anethole derivatives. The

Table 1. Effect of anethole and its derivatives on the vascular permeability assay

Treatment	Dose (mg/kg p.o.)	Amount of dye leakage (μg) mean ± SE ($n = 6$)	Inhibition (%)
Control	Saline	75.29 ± 5.5[a]	0
Vehicle	0.2 mL	68.61 ± 4.1[a]	8.8
1	30	68.35 ± 5.8[a]	9.2
1	300	63.24 ± 5.7[a]	16.0
2	30	57.48 ± 5.0[b]	23.6
2	300	41.99 ± 4.9[c]	44.2
3	30	37.46 ± 3.6[c]	50.2
3	300	26.02 ± 3.3[c]	65.4
4	30	32.31 ± 2.9[c]	57.1
4	300	42.04 ± 5.4[c]	44.4
Indometacin	10	28.30 ± 2.2[c]	62.5

Different small letters means significantly different from the control at $P < 0.05$.

cycloxygenase, a crucial enzyme in the inflammatory processes, can have its activity inhibited for some phenylpropanoides esters.[20] The inhibition of cycloxygenase is the main mechanism of action of the non-steriodal anti-inflammatory drug indometacin.[21] It was also demonstrated that phenylpropanoides esters in micromolar concentrations had antioxidant activity that was related with anti-inflammatory activity.[22] Studies suggest a relationship between oxidative processes and tissue damage in some pathological events[23,24] and demonstrated that some medicinal plants used in the Chinese traditional medicine that has anti-inflammatory effects also presents antioxidant effects.[25]

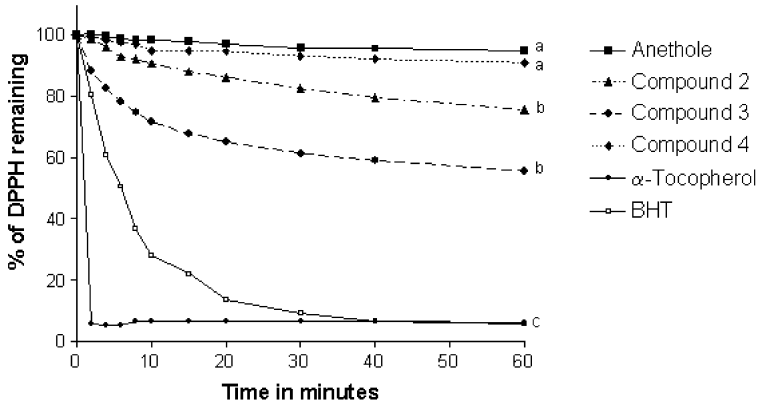

Figure 2. Antioxidant activity of the anethole and its derivatives on the DPPH test. Different letters means statistically significant differences at $P < 0.001$.

Table 2. Effect of anethole and its derivatives on gastric lesions induced by ethanol in mice

Treatment	Dose (mg/kg p.o.)	Gastric lesion index mean ± SE ($n = 6$)	Lesions inhibition (%)	Mucus weight (g) mean ± SE
Control	—	2.8 ± 0.44	0	0.030 ± 0.01[a]
Vehicle	—	2.4 ± 0.54	15	0.097 ± 0.14[a]
1	30	1.7 ± 0.5*	37	0.083 ± 0.11[a]
1	300	0.8 ± 1.3**	71	0.772 ± 0.42[b]
2	30	1.8 ± 0.83	35	0.060 ± 0.05[a]
2	300	1.2 ± 0.83*	57	0.022 ± 0.01[a]
3	30	1.8 ± 0.83	35	0.038 ± 0.01[a]
3	300	1.8 ± 0.83	35	0.028 ± 0.01[a]
4	30	2.2 ± 1.09	10	0.100 ± 0.17[a]
4	300	0.7 ± 0.54**	76	0.033 ± 0.02[a]
Ranitidine	100	1.0 ± 0.71*	64	0.023 ± 0.01[a]
Omeprazole	20	1.4 ± 1.14*	50	0.079 ± 0.09[a]

Significantly different from the control at $^{*}P < 0.05$ and $^{**}P < 0.001$.

Isoeugenol, eugenol and anethole present a methoxybenzene moiety and a propenyl group. The conjugated double bonds of anethole and isoeugenol are known for stabilizing the reactivity of the phenyl and benzyl groups and contribute for the antioxidant properties of these molecules.[6] Due to its antioxidant properties these compounds are strong candidates for intervene in inflammation mechanisms. Hydroxylated derivatives prepared in this study are stronger antioxidants than anethole and their anti-inflammatory action is higher therefore this study point out the correlation of these two activities.

Anethole and, in lesser extent, its derivatives **2** and **4** showed significant gastroprotector activity (Table 2). The majority of the substances that proceeding from natural products seems to act by different complementary mechanisms and many of them show mucous protective property.[26] These effects seem to be more related with factors that increase the protection of the mucous gastric from aggressive factors.[27–29] This study showed that anethole derivatives presented gastroprotector activity without modifying the mucus secretion, and only anethole in the 300 mg/kg dose activated the mucus gastric secretion.

The structural modifications made in the anethole molecule by the introduction of hydroxyl and *m*-chlorobenzoil groups had modified positively the anethole gastroprotector activity, however diminished significantly its mucus secretory activity, thus the double bond of the lateral chain of the anethole contributes to its gastroprotector activity and mucus secretor. On the other hand, the introduction of polar groups in the lateral chain of anethole increased its gastroprotector activity, but reduced its mucus secretor activity. However the introduction of two hydroxyl groups in the double of the lateral chain for the formation of **3**, modify the gastroprotector activity of anethole, since it did not present protective activity on the gastric mucus nor mucus secretory activity.

Table 3 displays the effect of the anethole and derivatives on the number of white blood cells of experimental animals, demonstrating that these compounds are safe for use in chosen concentrations.

3. Experimental

3.1. General methods

Chemicals were obtained from Sigma Chemical Co. (St. Louis, MO, USA), Aldrich Chemical Co. (Milwaukee, WI, USA), 2,2′-azobis (2-amidinopropane) dihydrochloride (ABAP) was from Wako Chemical GmbH (Neuss, Germany), TBA was from Merck (Darmstadt, Germany). TLC analyses were performed on a 3–10 cm aluminium sheet precoated with silica gel 60-254 (Merck) (solvent system: petroleum ether/ethyl ether 1:1). SiO_2, 200–400 mesh (Merck), was used for column chromatography. IR spectra were recorded on Perkin Elmer FT-IR spectrum 100 spectrophotometer and the values are expressed in cm^{-1}. NMR spectra were recorded on a Brucker Avance DPX-300 or DRX-500 spectrometer in $CDCl_3$ or appropriate solvent. Mass spectra were obtained using a Hewlett-Packard 5971 GC/MS instrument employing the following conditions: column: Dimethylpolysiloxane DB-1 coated fused silica capillary column (30 m × 0.25 mm); carrier gas: He (1 mL/min); injector temperature: 250 °C; detector temperature: 200 °C; column temperature: 35–180 °C at 4 °C/min then 180–250 °C at 10 °C/min; mass spectra: electron impact 70 eV.

3.1.1. 1-Hydroxy-1-(4-methoxyphenyl)-propane (2). This compound was prepared following the methodology described by Furniss et al.[30] with modifications as follows: $Hg(OAC)_2$ (10.78 g) and water (20 mL) were placed in a flask fitted with a efficient mechanical stirrer and a dropping funnel. After the acetate was dissolved, tetrahydrofuran (30 mL) was added quickly. The mixture was stirred for 15 min. Then anethole (5 g) was added and the reaction mixture was stirred at room temperature for 1 h. While stirring 3 M sodium hydroxide solution (100 mL) was added, followed by a solution of sodium borohydride (0.64 g) in 3 M sodium hydroxide (30 mL). The rate of addition was controlled and the temperature of the reaction mixture was maintained at 25 °C. This mixture was stirred vigorously at room temperature for 3 h and then allowed to remain overnight in a separator funnel. Mercury separated out from the aqueous alkaline phase and organic layer. The aqueous phase was saturated with sodium chloride, removed the additional

Table 3. Effect of the anethole and derivatives on the number of white blood cells

Treatment	Dose (mg/kg p.o.) $n = 6$	Before treatment	Number of leukocite at days after treatment (Mean ± SE)				
			3	6	9	12	15
Salina	0	4708 + 1471	3065 + 1072	4006 + 1155	3898 + 1154	3391 + 847	4314 + 1599
Tween 0.5%	0.2 mL	4700 ± 530	3390 ± 1152	3280 ± 975	2670 ± 719	3320 ± 542	4250 ± 1281
Anethole	30 mg/kg	5710 ± 2375	2680 ± 624	3840 ± 932	3700 ± 1393	3560 ± 1007	5760 ± 2327
Anethole	300 mg/kg	5180 ± 2033	3240 ± 954	3980 ± 1165	4210 ± 1374	3240 ± 837	4550 ± 2043
Anol	30 mg/kg	4780 ± 1291	3470 ± 1390	4150 ± 1274	4320 ± 860	3780 ± 949	3980 ± 753
Anol	300 mg/kg	5000 ± 1996	2720 ± 929	4190 ± 2452	4360 ± 1994	2880 ± 623	3800 ± 793
Diol	30 mg/kg	4290 ± 1057	2840 ± 317	3790 ± 791	3330 ± 583	4390 ± 876	3320 ± 1328
Diol	300 mg/kg	5040 ± 1228	2340 ± 722	4410 ± 614	4580 ± 850	3210 ± 726	5220 ± 2629
Ester-diol	30 mg/kg	4270 ± 803	3520 ± 1296	4050 ± 911	3960 ± 722	3390 ± 877	3900 ± 921
Ester-diol	300 mg/kg	3410 ± 687	3390 ± 1759	4370 ± 918	3960 ± 677	2750 ± 393	4050 ± 690

Student's *t*-test demonstrated no statistical differences among results ($P < 0.05$).

organic layer, which separated and extracted with ether (3×30 mL). The organic layer and the ether extracts were joined and washed with water (4×25 mL), dried over anhydrous sodium sulfate and the solvent removed by evaporation. The residue obtained was purified by silica gel column chromatography, eluted with petroleum ether and ethyl ether in mixtures of increasing polarity. The elution with petroleum ether/ethyl ether (1:1) afforded **2** (1.5 g).

3.1.2. 1-Hydroxy-1-(4-methoxyphenyl)-propane (2). Colourless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, $J = 8.5$ Hz, 2H, H-3, H-5), 6.87 (d, $J = 8.5$ Hz, 2H, H-2, H-6), 4.49 (t, $J = 6.6$ Hz, H-7), 3.79 (s, 3H, OCH_3), 1.80 (m, H-8a), 1.69 (m, H-8b), 0.88 (t, $J = 7.4$ Hz, CH_3-9); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.27 (C-1), 137.28 (C-4), 127.66 (C-3, C-5), 114.1 (C-2, C-6), 75.91 (C-7), 55.63 (OCH_3), 32.16 (C-8), 10.63 (C-9); IR (KBr) ν_{max}: 3400 (O–H), 3063 (C_{sp^2}–H), 1612, 1513, 1462 (skeletal aromatic bands), 1247, 1034, 1177, 1034 (C–O) cm^{-1}; MS (EI) *m*/*z*: 166, 137 (100%), 121, 107, 94, 77, 65.

3.1.3. 1,2-Dihydroxy-1-(4-methoxyphenyl)-propane (3) and 1-hydroxy-1-(4-methoxyphenyl)-2-*m*-chlorobenzoyl-propane (4). Dichloromethane solutions of anethole (22 g) and the *m*-chloroperbenzoic acid (30 g) were mixed and maintained under stirring for 24 h at 0 °C. After this time, dichloromethane was distilled and the product of the reaction was purified by silica gel column chromatography.[30] Two compounds were separated **3** (5 g) with petroleum ether/ethyl ether (4:1) and **4** (11 g) using petroleum ether/ethyl acetate (2:8).

3.1.4. 1,2-Dihydroxy-1-(4-methoxyphenyl)-propane (3). White solid, ^{1}HNMR ($CDCl_3$, 500 MHz) δ 7.24 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 2H), 4.27 (d, $J = 7.7$ Hz, 1H), 3.78 (s, 3H, OCH_3), 3.74 (m, H-8), 3.04 (s, 1H), 0.88 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5 (C-1), 133.8 (C-4), 128.2 (C-3, C-5), 114.2 (C-2, C-4), 79.2 (C-7), 72.4 (C-8), 55.5 (OCH_3), 18.9 (C-9); IR (neat): 3410, 3261, 3017, 2967, 2893, 1612, 1515, 1453, 1249, 1177, 1034, 829 cm^{-1}; MS (EI) *m*/*z*: 182, 137 (100%), 109, 94, 77.

3.1.5. 1-Hydroxy-1-(4-methoxyphenyl)-2-*m*-chlorobenzoyl-propane (4). Yellow liquid, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (s, H-2′), 7.93 (d, $J = 7.0$ Hz, 1H, H-6′), 7.5 (d, $J = 7.0$ Hz, H-4′), 7.38 (t, $J = 7.0$ Hz, H-5′), 7.32 (d, $J = 8$,4 Hz, H-3, H-5), 6.89 (d, $J = 8.4$ Hz, H-2, H-6), 5.33 (q, $J = 6.8$ Hz, H-8), 4.74 (d, $J = 6.8$ Hz, H-7), 1.19 (d, $J = 6.8$ Hz, H-9), 3.79 (s, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.3 (C-7′), 159.7 (C-1), 134.7 (C-3′), 134.6 (C-4), 133.4 (C-4′), 129.8 (C-2′), 128.7 (C-5′), C129,0 (C-3, C-5) 128.3 (C-6′), 76.7 (C-7), 75.8 (C-8), 55.4 (OCH_3), 16.5 (C-9); IR (neat): 3530, 3063, 2962, 1707, 1612, 1575, 1513, 1299, 1255, 1130, 1031, 829, 744 cm^{-1}; MS (EI) *m*/*z*: 320, 276, 174, 137 (100%), 109, 77.

3.2. Antioxidant assay

3.2.1. Free radical scavenging activity (DPPH) method. The procedure for DPPH (1,1-diphenyl-2-picrylhydrazyl) test was according to Yepez et al.[31] 0.1 mL of 10 mM

methanol solution of each sample was mixed with 3.9 mL of a 6.5×10^{-5} M methanolic solution of (DPPH) free radical and the absorbance was read twelve times during 1 h at 515 nm in a Speckol spectrophotometer. Methanol was as used as blanket. The absorbance of the DPPH radical solution was measured and represents 0 time in Figure 2.

3.3. Biological assays

Pharmacological tests were conducted with male Swiss mice weighting 25–30 g. The animals were maintained in a room with a 12 light/dark cycle. Food and water were freely available except for acute ulcerogenesis test. All tested compounds were suspended in a solution of Tween 80 (0.5%), and administered ip or p.o. in a volume of 0.2 mL. All animal experimentations have been conducted in accordance with the guideline for care and use experimental animal of Brazilian College of Experimental Animal (COBEA).

3.4. Anti-inflammatory test—vascular increasing permeability induced by acetic acid

The method of Whittle[32] was used. One hour after oral administration of the anethole and its derivatives (30 and 300 mg/kg), the mice were injected with 0.1 mL of 2% Evans blue (Sigma) in saline solution at the retroorbital plexus. Then 10 min after the iv injection of the dye solution, 0.4 mL of 0.5% (v/v) solution of acetic acid was injected ip After 20 min, the mice were killed by ether, and their peritoneal cavities were washed with 10 mL of distilled water. The combined washings and dye leaking were filtered through glass wool and 0.1 mL of 0.1 N NaOH solution was added to the flask. The absorption was measured at 590 nm (Speckol Spectrophotometer, Germany). The amount of dye was expressed as μg/30 g of mouse. Indometacin (10 mg/kg) was used as a reference drug, and the control group animals received the same experimental handling as those of the test groups except that the drug treatment was replaced with 0.2 mL saline or vehicle (0.2 mL of 0.5% Tween 80/distilled water).

3.5. Gastroprotector activity test—ulcerogenesis assay

The animals were left 24 h for acclimatization to animal room conditions and were maintained on standard pellet diet and H_2O ad libidum. The food was withdrawn 18 h before the experiment, but allowed free access of H_2O. For each group six mice were used. The test samples, anethole and its derivatives, were administered to animals in 30 or 300 mg/kg body weight dosage as a suspension in 0.2 mL of 0.5% Tween 80/distilled water. The control group was given vehicle and received the same experimental handling as those of the test group. As reference drugs, omeprazole (20 mg/kg) and ranitidine (100 mg/kg) were used. The method described by Robert[33] was employed with modification. Test sample was administered orally 1 h before the oral application of EtOH 100% (1 mL) to mice and 45 min later the animals were sacrificed with an over-dose of ether. The stomachs were removed and opened along the greater curvature, rinsed with tap water to remove gastric contents and blood clots and fixed between glasses to assess the formation of ulcers. The sum of length (mm) of all lesions for each stomach was used as the ulcer index (UI), and the inhibition percentage was calculated by the following formula: [(UI control − UI treated)/UI control)]/100.

3.6. Effect on total white blood cell count

Groups of Swiss mice ($n = 6$) were treated orally with 0.2 mL of anethole and its derivatives (30 or 300 mg/kg) for 5 days. Blood sample was collected from the retroorbital plexus before the treatment and every third day after the fifth and last dose of drug administration till 21 days. The total white blood cell count was determined using haematocytometer. The control group received saline (0.2 mL, p.o.).

3.7. Statistical analysis of data

Results were expressed as mean ± SEM. For statistical analysis in the vascular permeability assay and antioxidant activity, one-way ANOVA test was used follow by Dunnet's multiple comparison test. One way analysis of variance following Kruskal Wallis test was used in the gastric lesions induced by ethanol assay. Student's *t*-test was used for statistical analysis in the count of blood cells.

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