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Dietary fish oil sensitizes A549 lung xenografts to doxorubicin chemotherapy

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Abstract

A549 xenografts were allowed to grow in nude mice to about 5 mm in diameter, then diets were changed to modified AIN-76 diets containing 19% wt./wt. fish oil (FO) or 20% wt./wt. corn oil (CO). Ten days later dietary ferric citrate (0.3% wt./dry wt.) was added and doxoribicin (DOX) treatment (3.6 mg/kg i.v. each of the 5 days for 18 days) commenced. Treatment with DOX halted the growth of tumors in the CO fed mice. However, in those mice, which consumed FO or FO with ferric citrate, treatment with DOX caused significant tumor regression.

Keywords: Polyunsaturated fatty acids; Fish oil; Doxorubicin; A549 lung cancers

1. Introduction

Doxrubicin (DOX) is commonly used as a component of the chemotherapy regimen for the treatment of a wide variety of human cancers including adenocarcinomas, sarcomas, melanomas, leukemias, and lymphomas [13]. We and others [9,14,15,25,26] have proposed that use of polyunsaturated fatty acids (PUFAs) prior to chemotherapy, may sensitize cancers to the effects of a chemotherapeutic drug. In vitro studies indicate that addition of PUFA from fish oil, including eicosapentanoic and docasahexanoic acids, to the culture media, did increase the efficacy of the chemotherapeutic drug against different cancer cell types including: ZR-75-1 breast [5,6], transformed rat fibroblasts [1], L1210 leukemic cells [11], A549 lung, PC-3 prostate [5], THKE tumorigenic human kidney epithelial [19], and MDA-MB 231 breast cancer cells [14]. However, to date, in vivo studies on dietary PUFAs in addition to chemotherapy treatment have been limited to breast cancer cell types. We wanted to see if the concept of supplementation of the diet of xenograft bearing mice with the fatty acids of fish oil would increase the efficacy of treatment of other types of cancers.

In the study described in this brief report, human A549 lung cancer cells were implanted subcutaneously (s.c.) on the backs of nude mice. The tumors were allowed to grow to about 5 mm in diameter, then the diet was changed to include 20% corn oil or 19% fish oil/1% corn oil. The mice were fed the high oil diets for ten days to allow substitution of the dietary fatty acids into cellular membranes before treatments were initiated. The treatment was DOX at 3.8 mg/kg

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body weight i.v., once each five days with or without ferric citrate dietary supplementation. The extra iron was added to the diet with the idea that the iron would serve as a prooxidant to add to the prooxidation potential of DOX. It was found that there was significant tumor regression in the mice, which consumed fish oil diets before and during DOX treatment but not in the mice which consumed corn oil diets before and during DOX treatment. To our knowledge, this is the first report demonstrating that dietary fish oil can increase the efficacy of a chemotherapeutic drug against a human lung cancer xenograft.

2. Methods and materials

2.1. Tumor cells

A549 human lung cancer cells (American Type Culture Collection, Rockville, MD) were cultured for injection in nude mice. The culture medium was an enriched L15:SMEM base media supplemented with other factors as described previously [21].

2.2. Animals

Twenty-five male nude mice were allowed to acclimate for one week then were inoculated with tumor cells. The mice were housed under aseptic conditions (positive air pressure in a designated nude mouse room, cages, bedding, water and food were sterilized, cages had microisolator tops) in a temperature (24°C) and light controlled (12 h light per day) room. All mouse handling was carried out under a laminar flow hood. Our Institutional Animal Care and Use Committee approved all animal use and handling before commencing the experiment. The animal care facilities are accredited by the American Association for the Accreditation of Laboratory Animal Care.

2.3. Experimental design

Cultured A549 cells were harvested, rinsed and suspended in serum-free L15:SMEM culture medium. Cells in suspension were counted using a hemocytometer and the cell count was adjusted to 10^8/ml. The suspension was kept well mixed during the time of injection. A549 cells (5×10^6 cells in 0.05 ml of serum free media) were injected s.c. on the upper back of each mouse.

The experimental design for the tumor bearing mice is diagrammed in Fig. 1, day 0 is the day of change to the high corn oil or fish oil diets. Mice were fed a regular mouse chow diet while the tumors were allowed to grow to about 5-mm diameter. This allowed the tumors to become established as growing tumors in the host mice before onset of the experimental diets. The tumor bearing mice were then divided into groups and placed on diets based on the AIN-76A diet but modified to contain either 20% corn oil or 19% menhaden fish oil with 1% corn oil. Compositions of the experimental diets are listed in Table 1. One percent corn oil was included in the fish oil diet to prevent the complications of essential fatty acid deficiency. Fifteen mice received the high corn oil diet and 10 mice received the high fish oil diet. The mice were maintained on these diets for ten days to allow substitution of cellular membrane fatty acids before beginning treatment with DOX or DOX and ferric citrate. The diets were prepared weekly, individual daily portions for each cage were packaged and the packages were stored in sealed containers at −20°C to suppress spontaneous lipid peroxidation. The food was replaced daily to prevent consumption of oxidized lipids.

Treatment, defined as DOX alone or DOX with supplemental ferric citrate in the diet, was initiated after ten days on the corn oil or fish oil diets. Supplemental ferric citrate was added to the diet of five mice on the fish oil diet and five mice on the corn oil diet, at a rate of 0.3% of the dry weight of the food. An untreated control group of five mice continued on the corn oil diet. DOX was obtained as Adriamycin PFC (Pharmacia & Upjohn, Inc. Kalamazoo, MI) (doxorubicin hydrochloride for injection, USP) at a

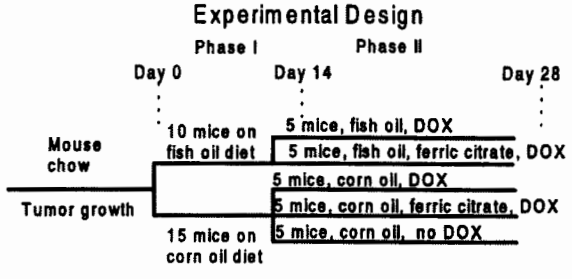

Fig. 1. Diagram of the experimental design.

Table 1
Composition of the diet by weight percent (g/100 g of food)

	Corn oil diet	Fish oil diet
Ingredient[a]		
Corn oil	20.0	1.0
Menhaden oil	–	19.0
Sugar	27.9	27.9
Casein	23.2	23.2
Cornstarch	17.4	17.4
AIN-76 vitamin mix[b]	1.15	1.15
AIN-76 mineral mix[b]	4.06	4.06
Choline bitartrate	0.23	0.23
DL-methionine	0.35	0.35
Cellulose	5.8	5.8
Total	100.1	100.1
Composition of the diets by % calories[c]		
Protein	20.6	20.6
Carbohydrate[d]	40.1	40.1
Fat	39.3	39.3
Energy content of each diet (kcal/g)	4.52	4.52

[a] Diet components and chemicals – Purified high nitrogen casein, pure corn starch, Alphacel (non-nutritive bulk cellulose) AIN-76 vitamin mixture, AIN-76 mineral mixture and choline bitartrate (99% pure) was obtained from ICN Nutritional Biochemicals, Cleveland, OH. Imperial brand (Sugarland, TX.) extra fine pure cane sugar and 100% pure corn oil (Wesson) was purchased locally. DL-methionine (cell culture, M.W. 149.2), menhaden fish oil and ferric citrate was purchased from Sigma, St. Louis, Missouri.

[b] α-Tocopherol is 0.02 g/100 g and ferric citrate (16–17% Fe^{3+}) is 0.02 g/100 g of the basal diet.

[c] Caloric content is calculated at 4 kcal/g for protein and carbohydrate and 9 kcal/g for fat. The diet which included a prooxidant (iron) had 0.3 g/100 g of ferric citrate (16–17% Fe^{3+}) added to the 19% MO or 20% CO diet.

[d] The % of calories from carbohydrate include the calories from sucrose, cornstarch and sucrose in the vitamin and mineral mix.

concentration of 2 mg/ml in the sterile isotonic solution. The DOX was stored under refrigeration and protected from light. A dose of 3.6 mg DOX/kg body weight (about 0.05 ml/ 28 g mouse) was injected into the lateral tail vein of the mice once each 5 days (days 10, 15, 20 and 25 after initiation of diet as in Fig. 2).

Tumor lengths and widths and body weights were measured three times weekly. Measurements were entered directly into an Excel spreadsheet. Tumor sizes were calculated using the formula for the volume of a prolate spheroid

$$V = 4/3 \times 3.14 \times L/2 \times W/2 \times D/2$$

The width measurement was used as the depth of the tumor. This shape was a good approximation of the shape of the tumors.

The experiment was terminated 18 days after the initiation of DOX treatment. The mice were anesthetized using a ketamine/S.A. rompun mixture (0.2 cm^3/ 25 g weight, IM) prepared by our Laboratory Animal Resources veterinarian, then killed by cervical dislocation. Mice in the untreated group consuming corn oil and the group consuming corn oil and treated with ferric citrate and DOX had to be killed early because of the large tumor size.

2.4. Statistical analyses

The growth of the tumors was divided into two phases: (1) phase I was defined as the 10 days during consumption of the corn oil or fish oil diets plus four days for initiation of a response to the treatment, (2) phase II, the final 14 days, was defined as the time of response to the treatment. Regression analysis for Phase II was started at day 14 rather than day 10 (the day of the first DOX injection), to allow time for response to DOX treatment to be reflected in a change in the tumor size. Linear regression analysis was used to determine if the change in the mean tumor size during Phase I or Phase II of the experiment showed a significant linear regression and to determine the slope (rate of growth of the tumor) of each linear regression. A significant positive slope indicated tumor growth, a significant negative slope indicated tumor regression and a non-significant slope

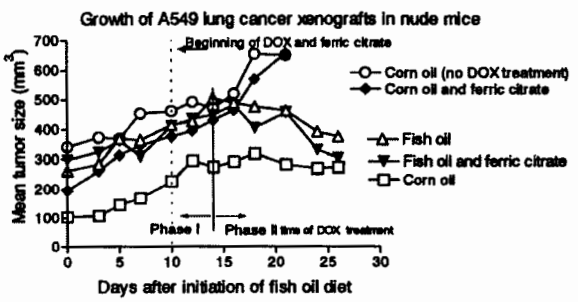

Fig. 2. Effects of experimental diets and DOX on growth of A549 lung cancer xenografts in nude mice (complete details under statistical analyses in text (Section 2.4).

indicated no growth. Slope analysis for differences between the regression of the mean tumor volume for each group during the first or second phase of the study was performed by PRISM and INSTAT software (GraphPad Software, San Diego, CA) using the general linear model procedure to generate an ANOVA. The ANOVA indicated that differences were present, thus a Tukey's multiple comparisons post test was conducted to determine differences between the slopes of each pair of lines against the null hypothesis that there was no difference between the slopes. A $P \leq 0.05$ was used to indicate that there was a significant difference between slopes of the regression lines and that the tumor growth rates represented by the slopes were significantly different.

3. Results

3.1. Body weight change

Table 2 lists the mean change in body weight between day 0 (initiation of the experimental diets) and day 28 (termination) of the experiment for each dietary group. The results of ANOVA of the body weight indicate that there were no significant differences in the mean change in body weight due to the diet or treatment of the mice. At this dose of DOX and on these diets, all groups gained weight over the course of the experiment. This indicates that the mice tolerated the diets and treatments equally well. There was no indication of diarrhea or gastric distress in any of the mice.

Table 2
The mean change in body weights of the groups of mice from day 0 (day of change to corn oil or fish oil diets) to day 20 of the experiment. DOX was initiated on day 10 in all groups except the 'no DOX group'

Final diet group ($n = 5$)	Mean (g) ± SD[a]
Corn oil	+5.6 ± 2.0
Fish oil	+4.8 ± 2.6
Corn oil + Fe	+4.8 ± 1.6
Fish oil + Fe	+4.2 ± 1.2
Corn oil; no DOX	+3.3 ± 0.7

[a] ANOVA showed that there were no significant differences in the change in body weight due to the diet or treatment of the mice.

3.2. Tumor growth

Fig. 2 is a graph of the mean tumor size over the time of the experiment. Day 0 is the day that the diets of the mice were changed to the high corn oil or high fish oil diets. The slope of the mean tumor size of each group was determined between day 0 and day 14 (Phase I) and from day 14 to day 28 (Phase II). Slopes of the linear regression for each group and results of ANOVA are reported in Table 3. A summary of the results of ANOVA and Tukey's multiple comparisons test of the tumor growth rates follows:

(1) There was not a significant difference in the rate of growth of the tumor due to the diet composition during phase I of the experiment, regardless of whether the mice were consuming 20% corn oil or 19% fish oil plus 1% corn oil in the diet. Thus, supplementation of the diet with fish oil did not significantly alter growth of this tumor prior to the treatment with DOX or DOX plus iron;
(2) The type of oil in the diet, however, did make a significant difference in the efficacy of DOX treatment. Specifically, DOX halted the growth of the tumors in the group of mice consuming corn oil,

Table 3
Growth rate of A549 human lung tumors (mean mm^3 per day + SD of slope)

Final diet/treatment group ($n = 5$)	Phase I[a]	Phase II
Corn oil; DOX	14.8 ± 1.9	−1.5 ± 1.8[b]
Fish oil; DOX	16.2 ± 1.8	−11.1 ± 1.5[b]
Corn oil + iron; DOX	15.9 ± 1.3	34.1 ± 4.2[b]
Fish oil + iron; DOX	11.2 ± 2.3	−13.1 ± 4.2[b]
Corn oil; no DOX	14.9 ± 2.0	14.9 ± 2.0[b]

[a] Linear regression analyses showed that during phase I, all slopes were significantly different from 0. ANOVA of the slopes showed that the growth rates of the tumors (slopes) were not significantly different from each other during Phase I, when mice were consuming either a corn oil or a fish oil diet without added iron and without DOX treatment.

[b] Linear regression analyses showed that the tumor growth rate(-slope of the regression line) of the group of mice which consumed corn oil and was treated with DOX was not significantly different from a slope of 0. The tumor growth rate of all other groups was a significant positive or negative slope. ANOVA followed by Tukey's multiple comparisons test of the slopes showed that growth rates (slopes) with the same letter are not significantly different, growth rates with different letters are significantly different.

that is, the slope of the regression line for the growth of these tumors was not significantly different from zero (a horizontal line indicates no growth over the time of treatment). However, the tumors in the mice consuming fish oil and being treated with DOX significantly regressed, that is, the slope of the linear regression line for this group was significantly negative;

(3) The type of oil in the diet made a significant difference when the treatment was a combination of supplemental iron and DOX. In the mice fed corn oil, the tumor continued to grow when the treatment was iron and DOX. However, in the mice fed fish oil, the tumors significantly regressed when the treatment was iron and DOX.

4. Discussion

In this brief report, we provide evidence that the efficacy of doxorubicin against A549 lung cancer xenografts was significantly increased when the AIN-76 diet formula (Table 1) was supplemented with fish oil and that there were no observed harmful side effects to the mice due to the consumption of fish oil. There was some unavoidable variation in the mean tumor size at the time of initiation of the diet. However, as shown in Table 3, the tumor growth rate of the group with the largest tumors (group 5) and of the group with the smallest tumors (group 1), both fed the corn oil diet, were not significantly different indicating that mean tumor size at the time of the diet change did not significantly alter the tumor growth rate. The effect of consumption of fish oil in the diet in the absence of DOX can be evaluated using the portion of the tumor growth curve analyzed prior to initiation of DOX treatment. There was no significant difference in growth rates between the groups which consumed corn oil and those which consumed fish oil. Thus, neither fish oil alone nor the differences in tumor size at the time of diet change, significantly altered the growth rate of this tumor model prior to the initiation of DOX or DOX and iron treatment.

The data show that, in mice fed corn oil, DOX inhibited growth of, but did not cause regression of, the tumors. This indicates that the tumor cells were either growth arrested and/or that only a fraction of the tumor cell population was killed by the DOX. However, DOX did not inhibit growth of tumors of mice fed corn oil with iron. A possible explanation for these results is that in the presence of dietary corn oil, tumor cells that were not killed by DOX treatment had their growth stimulated by the iron in the diet.

Unfortunately, we do not have adequate data to evaluate how the fish oil worked to suppress tumor growth. However, other reports do provide clues to how fish oil works to increase the efficacy of DOX chemotherapy. For example, increased lipid peroxidation in the tumor is one likely mechanism for the increased efficacy of DOX following consumption of fish oil. One mechanism of action for DOX is the formation of DOX-metal complexes and the production of free radical complexes [13]. The results of a number of reports show that membrane fatty acids of normal tissues [7,18,23,24,26] and of tumors [7], become more unsaturated when the mice consume fatty acids from fish oil instead of corn oil. Providing the PUFA substrate in the cell membranes would be expected to increase the generation of free radicals and would be expected to increase the oxidative damage from these free radicals. In fact, the increased unsaturation of membrane lipids was associated with increased lipid peroxidation and decreased tumor growth in MDA-MB 231 xenografts treated with edelfosine (Hardman et al., unpublished results) or in MX-1 xenografts treated with DOX compared to mice fed corn oil [26].

Other mechanisms have also been proposed to account for the suppression of cancer growth by fish oil or combinations of fish oil and a drug. These mechanisms include:

(1) Decreased levels of PGE_2 following dietary fish oil [16,28]. Decreased PGE_2 is associated with increased immune activity [17] and decreased tumor promotion and growth [12];

(2) Decreased activity of protein kinase C (PKC), which has been associated with reversal of drug resistance [10] and slowed angiogenesis (reviewed in [20]).

In addition, the n-3 fatty acids of fish oil have been shown to be beneficial to the patient by suppressing cancer cachexia [3,4,22,27] and by improving the response to radiotherapy [10]. Bougnoux et al. has reported that an increased amount of n-3 fatty acids in the composition of adipose tissue was associated

with better response to chemotherapy in breast cancer patients [8]. Atkinson et al. has reported that dietary docosahexanoic acid (22:6n-3) slowed tumor growth and enhanced bone marrow cellularity of mice injected with fibrosarcoma cells [2]. Use of the n-3 fatty acids derived from fish oil as an adjuvant to therapy has the potential to increase the efficacy of the chemo- or X-radiation therapies in current use. Our future studies will be designed to provide adequate tumor tissue at sacrifice time to investigate the mechanisms of n-3 fatty acids to increase the efficacy of cancer therapy. This information about the mechanisms of action of n-3 fatty acids will allow us to devise even more effective cancer treatment strategies.

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References

[1] T.G. Atkinson, K.A. Meckling-Gill, Regulation of nucleoside drug toxicity by transport inhibitors and omega-3 polyunsaturated fatty acids in normal and transformed rat-2 fibroblasts, Cell. Pharmacol. 2 (1995) 259–264.

[2] T.G. Atkinson, L. Murray, D.M. Berry, D.J. Ruthig, K.A. Meckling-Gill, DHA feeding provides host protection and prevents fibrosarcome-induced hyperlipidemia while maintaining the tumor response to AraC in Fischer 344 rats, Nutr. Cancer 28 (1997) 225–235.

[3] M.D. Barber, J.A. Ross, A.C. Voss, M.J. Tisdale, K.C.H. Fearon, The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer, Br. J. Cancer 81 (1999) 80–86.

[4] S.A. Beck, K.L. Smith, M.J. Tisdale, Anticachectic and antitumor effect of eicosapentaenoic acid and its effect on protein turnover, Cancer Res. 51 (1991) 6089–6093.

[5] M.E. Begin, G. Ells, U.N. Das, D.F. Horrobin, Differential killing of human carcinoma cells supplemented with n-3 and n-6 polyunsaturated fatty acids, J. Natl. Cancer Inst. 77 (1986) 1053–1062.

[6] M.E. Begin, G. Ells, D.F. Horrobin, Polyunsaturated fatty acid-induced cytotoxicity against tumor cells and its relationship to lipid peroxidation, J. Natl. Cancer Inst. 80 (1988) 188–194.

[7] C.E. Borgeson, L. Pardini, R.S. Pardini, R.C. Reitz, Effects of dietary fish oil on human mammary carcinoma and on lipid-metabolizing enzymes, Lipids 24 (1989) 290–295.

[8] P. Bougnoux, V. Chajes, B. Hubert, E. Germain, C. Lhuillery, S. Saez, G. Calais, N-3 polyunsaturated fatty acids and chemosensitivity of breast carcinoma, Proc. Am. Assn. Cancer Res. 36 (1995) 327.

[9] C.P. Burns, A.A. Spector, Membrane fatty acid modifications in tumor cells: potential therapeutic adjunct, Lipids 22 (1987) 178–184.

[10] U.N. Das, G. Madhavi, G.S. Kumar, M. Padma, P. Sangeetha, Can tumour cell drug resistance be reversed by essential fatty acids and their metabolites? Prostaglandins Leukotrienes Essent. Fatty Acids 58 (1998) 39–54.

[11] H.M. de Salis, K.A. Meckling-Gill, EPA and DHA alter nucleoside drug and doxorubicin toxicity in L1210 cells but not in normal murine S1 macrophages, Cell. Pharmacol. 2 (1995) 69–74.

[12] C.E.E. de Vries, C.J.F. Van Noorden, Effects of dietary fatty acid composition on tumor growth and metastasis, Anticancer Res. 12 (1992) 1513–1522.

[13] R.T. Dorr, D.D. Von Hoff, Cancer Chemotherapy Handbook, Appleton & Lange, CT, (1994).

[14] W.E. Hardman, C.J. Barnes, C.W. Knight, I.L. Cameron, Effects of iron supplementation and ET-18-OCH3 on MDA-MB 231 breast carcinomas in nude mice consuming a fish oil diet, Br. J. Cancer 76 (1997) 347–354.

[15] W.E. Hardman, M. Moyer, I.L. Cameron, Fish oil supplementation enhanced CPT-11 (Irinotecan) efficacy against MCF7 breast carcinoma xenografts and ameliorated intestinal side effects, Br. J. Cancer 81 (1999) 440–448.

[16] G. Hornstra, A.C. van Houwelingen, G.A.A. Kivits, S. Fischer, W. Uedelhoven, Dietary fish and prostanoid formation in man, Adv. Prostaglandin Thromboxane Leukotrienes. Res. 21 (1990) 225–228.

[17] D. Hwang, Essential fatty acids and immune response, FASEB J. 3 (1989) 2052–2055.

[18] W.E.M. Lands, A. Morris, B. Libelt, Quantitative effects of dietary polyunsaturated fats on the composition of fatty acids in rat tissues, Lipids 25 (1990) 505–516.

[19] L. Maehle, E. Eilertsen, S. Mollerup, S. Schonberg, H.E. Krokan, A. Haugen, Effects of n-3 fatty acids during neoplastic progression and comparison of in vitro and in vivo sensitivity of two human tumour cell lines, Br. J. Cancer 71 (1995) 691–696.

[20] M.F. McCarty, Fish oil may impede tumour angiogenesis and invasiveness by down-regulating protein kinase C and modulating eicosanoid production, Med. Hypotheses 46 (1996) 107–115.

[21] M.P. Moyer, J.B. Aust, Human colon cells: culture and in vitro transformation, Science 224 (1984) 1445–1447.

[22] S.A. Price, M.J. Tisdale, Mechanism of inhibition of a tumor lipid-mobilizing factor by eicosapentaenoic acid, Cancer Res. 58 (1998) 4827–4831.

[23] B.S. Reddy, S. Sugie, Effect of different levels of omega-3 and omega-6 fatty acids on azoxymethane-induced colon carcinogenesis in F344 rats, Cancer Res. 48 (1988) 6642–6647.

[24] D.P. Rose, J. Rayburn, M.A. Hatala, J.M. Connolly, Effects of

dietary fish oil on fatty acids and eicosanoids in metastasizing human breast cancer cells, Nutr. Cancer 22 (1994) 131–141.
[25] Y. Shao, J. Hull, L. Pardini, R.S. Pardini, Dietary menhaden oil improves the therapeudic index of cyclophosphamide and 5-fluorouracil towards MX-1 human mammary carcinoma in athymic mice, Proc. Am. Assn. Cancer Res. 38 (1997) 110.
[26] Y. Shao, L. Pardini, R.S. Pardini, Dietary menhaden oil enhances mitomycin C antitumor activity toward human mammary carcinoma MX-1, Lipids 30 (1995) 1035–1045.
[27] M.J. Tisdale, Mechanism of lipid mobilization associated with cancer cachexia: interaction between polyunsaturated fatty acid, eicosapentaenoic acid and inhibitory guanine nucleotide-regulatory protein, Prostaglandins Leukotrienes Essent. Fatty Acids 48 (1993) 105–109.
[28] P.C. Weber, A. Sellmayer, Modification of the prostanoid system and cell signalling by precursor fatty acids, Adv. Prostaglandin Thromboxane Leukotrienes. Res. 21 (1990) 217–224.