CAPÍTOL 9. DISCUSSIÓ

El caràcter protector o inhibidor de l'oli de peix, principal font d'AGPI de la sèrie n3, sobre la carcinogènesi colònica ha estat àmpliament estudiada en el darrers temps.[75,94,266,312,395,403,407,485,486] En humans, l'oli de peix, tant a individus sans com a individus amb adenomes colònics, s'associa a un descens de la proliferació cel lular al recte.[11,12,28] D'altra banda, l'efecte de l'oli d'oliva sobre la carcinogènesi colorectal ha estat escassament avaluat. Els resultats obtinguts en aquest estudi mostren com una dieta normolipídica (5%) basada en l'oli d'oliva té efectes anticarcinogènics, similars als observats amb els AGPI de la sèrie n3, en un model de carcinogènesi induïda químicament.

La possibilitat d'avaluar els primers estadis oncogènics és de gran interès alhora de simplificar el disseny experimental als estudis de carcinogènesi amb animals. En aquesta Tesi, s'ha escollit la formació de FCA com a biomarcador per valorar les alteracions que poden succeir a la fase d'iniciació oncogènica.[155,222,382] Recentment, els FCA han estat considerats com a veritables lesions preneoplàsiques colòniques tant en animals com en humans.[299,379,488] Malgrat això, estudis amb inhibidors de la carcinogènesi no sempre han previngut la formació de FCA en animals.[24] Aquesta aparent discrepància pot relacionar-se tant amb diferències entre els models de carcinogènesi experimental emprats, com amb la cadència d'aplicació del carcinogen. En qualsevol cas, en el present estudi, s'ha intentat relacionar els resultats obtinguts en els estadis inicials per mitjà del biomarcador premaligne esmentat (FCA) amb els observats en les darreres fases de desenvolupament tumoral al còlon. Aquest plantejament de l'estudi aporta una aproximació prudent a la modulació temporal del procés carcinogènic colònic per mitjà del greix dietètic. Concretament, les dietes amb oli de peix (grup n3) i amb oli d'oliva (grup n9) van inhibir de forma significativa tant la formació de FCA a la setmana 12 de l'estudi com el posterior desenvolupament dels tumors colònics a la

setmana 19 en comparació als animals alimentats amb una dieta que conté oli de càrtam com a component greixós (grup n6). De fet, l'efecte modulador del greix dietètic sobre l'oncogènia colorectal es manifestà de forma paral lela pel que fa al nombre de FCA i a l'aparició de tumors. Així doncs, les evidències obtingudes suggereixen la possibilitat de que els FCA puguin ser considerats com a biomarcadors predictius del posterior desenvolupament tumoral en les condicions utilitzades en aquest estudi.

La formació dels FCA hauria de ser considerada de forma independent a la multiplicitat o creixement d'aquests (nombre de CA per focus); és a dir, mentre que poden existir factors que actuïn suprimint l'aparició de CA individuals, altres poden actuar prevenint el creixement dels FCA més petits.[24] En relació amb això, en aquest estudi s'observà un descens similar en la formació de FCA i en el nombre total de CA per les dietes n9 i n3 (**figura 8.3.A**). Malgrat això, l'estudi de la multiplicitat, i per tant del creixement dels FCA revelà que la reducció en el nombre d'aquestes formacions preneoplàsiques en els animals alimentats amb la dieta n9 fou deguda fonamentalment a una reducció dels FCA d'una i dos CA, mentre que pels animals alimentats amb la dieta n3 el descens és degut, principalment, als FCA integrats per quatre CA (**figura 8.3.B**). Aquesta diferent regulació en la formació dels FCA no es traduí amb una diferent malignificació o desenvolupament carcinogènic a ambdós grups. En aquest sentit, un recent estudi mostrà que el nombre de CA per focus no constitueix un factor predictiu del posterior desenvolupament tumoral al colon.[542] Les diferències observades a la mida o multiplicitat dels FCA entre les rates alimentades amb la dieta n3 i les alimentades amb la dieta n9 suggereixen que aquests AG actuen sobre diferents fases en la formació i creixement dels focus; així doncs, propers estudis haurien de considerar l'avaluació conjunta d'ambdues famílies d'AG, n3 i n9, amb l'objectiu d'esbrinar la possibilitat d'un sinergisme en el guariment de la carcinogènesi colorectal.

Junt amb la incidència i multiplicitat tumoral, el grau de diferenciació histològica dels tumors també es mostrà influenciat per la composició del greix de la dieta. Malgrat que estudis previs mostraren resultats contradictoris respecte a l'efecte dels AG de la sèrie n3 sobre el grau de diferenciació tumoral; recentment, s'ha observat que l'administració d'AGPI n3, ja sigui com a component dietètic o en forma de suplementació orogàstrica, comporta una millora del grau de la diferenciació tumoral en rates tractades amb carcinogen o a les que se'ls hi va practicar una anastomosi colorectal.[94,197,485] Aquestes evidències contrasten amb un treball previ on, malgrat que l'administració dietètica d'EPA disminuïa l'aparició de tumors, aquests no foren tan ben diferenciats com els que aparegueren als animals alimentats amb una dieta que contenia AG de la sèrie n6.[312] En tot cas, les observacions derivades del present estudi van en la línia dels estudis més recents, on l'efecte de dietes amb AGPI n3 comporten una millora del grau de diferenciació tumoral respecte als AGPI de la sèrie n6. D'altra banda, una de les aportacions notables d'aquesta Tesi és l'efecte significatiu de l'oli d'oliva, font dels AG de la sèrie n9, sobre el grau de diferenciació tumoral, una troballa no descrita amb anterioritat.

Així doncs, els efectes beneficiosos dels AG de la sèrie n9 i de la sèrie n3 suggereixen la intervenció d'aquests AG sobre la proliferació, diferenciació i/o apoptosi cel lular. Aquestes accions podrien estar relacionades amb la regulació, a nivell molecular, d'una gran varietat de senyals intracel lulars entre les que destaca la complexa regulació per part de diferents famílies lipídiques dels isoenzims de PKC en el marc de la carcinogènesi colorectal.[95,121,122] En relació això, recentment s'ha observat l'aparició de fenòmens prooncogènics associats a la PKC-βII, i s'ha suggerit que determinats factors dietètics, com els AGPI n3, poden bloquejar l'expressió d'aquest isoenzim, principalment a la meitat distal colònica de les rates tractades amb AOM.[121] Al present estudi , l'aparició preferent dels tumors a la meitat distal a les rates alimentades amb oli de peix o de càrtam, a diferència de les alimentades amb oli d'oliva, podria relacionar-se amb un nivell

regulació molecular similar al esmentat a l'estudi anterior. En qualsevol cas, els mecanismes moleculars i cel lulars relacionats amb la carcinogènesi colònica i la seva regulació per part dels diferents AG haurà d'ésser motiu de propers estudis.

La suplementació amb oli de peix, fins i tot a dosis baixes, comporta un increment significatiu dels nivells d'AGPI de la sèrie n3 i un descens de la proliferació cel lular a la mucosa rectal tant a voluntaris sans com individus amb un elevat risc de patir una neoplàsia colònica.[11,28] Els efectes antitumorals associats a l'oli de peix han estat atribuïts al contingut de l'EPA més que a l'DHA.[68] En relació amb això, s'ha descrit un descens del contingut d'EPA a les lesions neoplàsiques de còlon a mesura que evoluciona la seqüència adenoma carcinoma.[157] D'altra banda, hi ha estudis que han suggerit que els efectes sobre la carcinogènesi per manipulació dietètica del contingut d'AG a la mucosa colorectal es basa principalment en l'alteració del quocient AA/EPA. Concretament, malgrat la suplementació amb oli de peix, no s'han observat efectes antiproliferatius en individus sans que presentaven una elevada ingesta dietètica d'AG de la sèrie n6, probablement degut a que tot i augmentar el contingut d'EPA, la taxa AA/EPA a la mucosa colorectal no disminuí.[28] Conseqüentment, l'objectiu de les intervencions dietètiques sobre la carcinogènesi colorectal podria ser la consecució d'un descens en la proporció AA/EPA més que un augment de la concentració d'EPA a la mucosa. D'altra banda, la capacitat antitumoral de l'oli d'oliva s'ha atribuït fonamentalment a l'àcid oleic, que pot arribar a constituir el 75% del contingut total d'AG d'aquest oli. El present estudi mostra com la dieta n9 comporta un descens tant en la concentració d'AA com en la proporció AA/EPA respecte a la dieta n6, el que pot representar un factor associat als efectes beneficiosos de l'oli d'oliva. Ara bé, s'ha de considerar que l'oli d'oliva esta integrat per altres substàncies que poden tenir una activitat quimioprotectora sobre la carcinogènesi colorectal. Concretament, constituents de l'oli d'oliva com α-tocoferol, β-carotè, polifenols o l'esqualè mostren una marcada capacitat antitumoral en models de carcinogènesi experimental colònica.[332,352,393,535] En

aquest sentit, un recent estudi observà com un 1% d'esqualè era capaç de suprimir la formació de FCA així com la multiplicitat d'aquests (nombre de criptes per FCA) en un model experimental de carcinogènesi colònica.[393] Per tant, un altre component de l'acció beneficiosa de l'oli d'oliva podria ser l'esqualè, ja que aquest constituí el 0,8% en l'oli d'oliva utilitzat en aquest estudi.

L'àcid oleic també constitueix entre el 30% i el 45% del greix de bòvids i de l'aviram, així com d'altres greixos vegetals com l'oli de blat de moro (30%), l'oli de soia (23-25%) i l'oli de gira-sol (16-30%).[332] Aquests greixos i olis, amb un contingut intrínsec d'àcid oleic, mostren característiques procarcinogèniques en models animals induïts químicament, el que ha fet pensar en una manca de relació entre els efectes beneficiosos de l'oli d'oliva i l'àcid oleic. No obstant això, s'ha de considerar que els olis i greixos esmentats aporten principalment AGS i àcid linoleic, i la seva administració provoca un augment en el contingut d'AA a la mucosa colònica que fa incrementar la taxa AA/EPA.

Els mètodes per avaluar el paper dels eicosanoides a la carcinogènesi colorectal inclouen tot un seguit d'assaigs *in vitro* com la determinació de la concentració de PGE_2 en homogenats de la mucosa colònica,[312] formació de PGE_2 a partir de cultius primaris de biòpsies,[28] i mesura de l'activitat de la ciclooxigenasa de la mucosa colònica a partir de ^{14}C-AA.[395] Aquests tipus d'assaigs poden implicar una alteració dels resultats finals per la natura dels eicosanoides amb una vida mitja reduïda i amb una producció instantània com a resposta a un trauma sobre el teixit. Un exemple d'això és l'activació de les fosfolipases generada al practicar una biòpsia a la mucosa colònica o per la manipulació en cultius tisulars.[141,412,544] La diàlisi intracolònica és un mètode poc traumàtic i ha estat considerat com la tècnica més apropiada per mesurar el balanç entre els eicosanoides produïts i els degradats. De fet, la diàlisi intracolònica ha estat àmpliament utilitzada per mesurar la producció d'eicosanoides a la colitis humana i experimental.[40,267-269,391,545] El líquid de diàlisi recull la producció d'eicosanoides de l'intestí adjacent

sense que hi hagi una contribució de secrecions procedents d'altres parts del budell.[391,545] D'altra banda, donat que el temps de diàlisi va ésser d'una hora, les mesures fetes sobre la producció intracolònica dels eiocosanoides podrien ser menystingudes; malgrat això, el temps adoptat evita la formació artificial d'eicosanoides per l'efecte irritant de la bossa de diàlisi. Les concentracions dels eicosanoides obtingudes a partir de la diàlisi intracolònica van revelar un augment significatiu en la producció de PGE_2 i LTB_4 en els animals del grup dietètic n6 tractats amb carcinogen en comparació amb altres grups dietètics. A més, les correlacions fetes amb la concentració d'AA de la mucosa colònica suggereixen que els resultats són una bona estimació de la producció local d'aquests eicosanoides, menyspreant les possibles aportacions de la microflora bacteriana.

Tal i com s'ha esmentat anteriorment, un possible mecanisme pel que els AG de les sèries n3 i n9 exercirien els efectes antitumorals es basaria en la capacitat d'influenciar el metabolisme de l'AA. En aquest estudi, l'administració de les dietes que contenen oli d'oliva (n9) i oli de peix (n3) mostren una reducció dels nivells d'AA a la mucosa colorectal, tant a la setmana 12 com a la setmana 19, en comparació amb el grup dietètic on el greix prové de l'oli de càrtam (n6). L'AA és el precursor d'eicosanoides bioactius: prostaglandines dienoiques i leucotriens tetraenoics. Assaigs *in vitro* han mostrat la capacitat d'estimular la proliferació de cèl lules cancerígenes per part de la PGE_2 i del LTB_4,[51,385] al contrari del que succeí pel LTB_5. Addicionalment, s'ha suggerit la capacitat de la PGE_2 i del LTB_4 d'inhibir l'apoptosi.[344,444,503] Estudis tant en humans com en animals han revelat un increment als nivells de PGE_2 als teixits colònics afectats per lesions neoplàsiques.[36,187,383,395] De la mateixa manera, la inhibició de la producció d'eicosanoides per antiinflamatoris no esteroidals, tant en humans com en models experimentals, sembla associar-se a un descens en el risc de desenvolupar un carcinoma colònic.[25,111,180,260,402,464,500] S'ha suggerit que els AGPI de la sèrie n3 exerceixen els efectes antioncogènics per la substitució competitiva a les membranes cel lulars de l'AA i per l'addicional descens en la producció

d'eicosanoides derivats d'aquest AG.[28,68,312,395] Els resultats del present estudi recolzen les observacions dels treballs anteriors pel que fa al descens en la producció intracolònica de PGE_2 i LTB_4 en els animals del grup dietètic n3 respecte als del grup n6. Concretament, s'observà un augment significatiu en la producció intracolònica de PGE_2 en els animals del grup n6 tractats amb AOM respecte als tractats amb sèrum fisiològic, mentre que en el grup n3 s'observà una disminució dels nivells d'aquesta prostaglandina als animals tractats amb el carcinogen en comparació als controls. Aquests resultats són similars als observats en un estudi anterior,[395] excepte pel que fa als animals alimentats en oli de peix on els nivells de PGE_2 es mostraren més elevats a la mucosa colònica dels animals tractats amb AOM que als controls. Ara bé, entre ambdós estudis apareixen una sèrie de diferències com són la quantitat de greix que contenen les dietes, el règim d'aplicació del carcinogen i el mètode d'avaluació de la producció dels eicosanoides que podrien justificar, si més no, les aparents discrepàncies aparegudes. D'altra banda, tal i com s'ha esmentat, la producció intracolònica de LTB_4 s'observa significativament elevada en les rates tractades amb AOM del grup dietètic n6 respecte a les del grup dietètic n3 i n9. En aquest sentit, el present estudi aporta una informació addicional pel que fa a la influència de les diferents famílies d'AG sobre la producció *in vivo* de LTB_4 en un model experimental de carcinogènesi colorectal.

Als animals alimentats amb oli d'oliva, la producció intracolònica dels eicosanoides va romandre inalterable davant l'aplicació del carcinogen, sent els nivells observats, principalment pel que fa a la PGE_2, similars als del grup n3. Així doncs, la substitució competitiva de l'AA a les membranes cel lulars per AG de la sèrie n9 pot associar-se a un bloqueig en la producció intracolònica de PGE_2. En aquest sentit, l'efecte beneficiós de l'oli d'oliva sobre la carcinogènesi colorectal podria estar relacionat en part amb la inhibició de la producció d'eicosanoides bioactius.

D'altra banda, malgrat que els eicosanoides derivats de l'EPA han estat considerats biològicament menys actius,[83,234,324,483] l'efecte d'aquests sobre la transformació cel lular és desconegut. Aquest estudi aporta informació sobre la producció intracolònica de metabòlits derivats de l'EPA en un model de carcinogènesi experimental. En aquest sentit, s'observa com un fet relativament sorprenent, el decrement en la producció de PGE_3 en les rates del grup n3 induïdes amb carcinogen respecte als altres grups i respecte als controls. Aquesta evidència, junt al descens de la PGE_2 en aquest mateix grup dietètic, suggereix l'existènica d'un bloqueig en el metabolisme ciclooxigenàsic per part dels AGPI n3, tal i com s'ha suggerit prèviament en treballs fets en cultius cel lulars.[71,324] Pel que fa al metabolisme lipoxigenàsic, la producció de LTB_5, al contrari del que succeïa amb el LTB_4, no va alterar-se per l'aplicació del carcinogen en el grup n3. D'altra banda, s'observaren nivells elevats de LTB_5 al grup n6. L'explicació d'aquesta troballa podria ser l'existència d'un alt rendiment metabòlic de la 5-LOX al grup dietètic n6; mentre que al grup n3, l'elevada presència d'EPA i/o un excés de productes finals del seu metabolisme lipoxigenàsic podria comportar l'aparició de inhibicions per *feed-back* negatius sobre els enzims.[377] Així doncs, l'augment d'EPA a la mucosa colònica produït per la ingesta d'oli de peix, podria associar-se tant a un bloqueig del metabolisme ciclooxigenàsic com lipoxigenàsic, que podria estar implicat en mecanismes d'inhibició de la carcinogènesi colònica observats amb els AGPI de la sèrie n3. Aquesta regulació dels enzims lipoxigenàsics i ciclooxigenàsics per l'alteració en la proporció AA/EPA a la mucosa colònica també podria explicar, si més no parcialment, la síntesi pràcticament inalterable d'eicosanoides en les rates alimentades amb l'oli d'oliva vers a la carcinogènesi colònica.

Finalment, atribuir l'efecte beneficiós de l'oli de peix i de l'oli d'oliva sobre la carcinogènesi colorectal a la modulació de la producció d'eicosanoides pot suposar una visió limitada de la veritable complexitat d'acció dels AG. A la literatura apareixen multitud d'exemples que argumenten a favor d'altres nivells de

regulació, particularment dels AGPI n3, com: efectes sobre l'expressió d'oncogens,[21,123,493] apoptosi,[94,95,266,392] i senyals de transducció intracel lulars.[96,121,224,327,395,403] Per tant, caldrà avaluar si els AG de la sèrie n9 participen en la modulació d'aquests o altres mecanismes i si la seva modulació influencia el desenvolupament neoplàsic al còlon.

CAPÍTOL 10. CONCLUSIONS

1. L'administració d'una dieta amb un 5% d'oli d'oliva com a component greixós té un efecte protector sobre el desenvolupament oncogènic en un model experimental de carcinogènesi colònica, tant a les fases inicials (FCA) com a les tardanes (tumors).

2. Aquest efecte beneficiós de l'oli d'oliva es similar a l'observat per l'oli de peix i contrasta amb els efectes protumorals de l'oli de càrtam.

3. L'oli d'oliva mostra un efecte beneficiós sobre la diferenciació tumoral més marcat que l'observat amb l'oli de peix.

4. L'efecte de dietes amb diferent contingut greixós sobre la carcinogènesi colònica podria ésser explicat, en part, per la modulació del metabolisme de l'AA i la síntesi d'eicosanoides:

- En primer lloc, s'observà un augment d'EPA en relació amb l'AA a la mucosa colònica dels animals alimentats amb les dietes n3 i n9, però no amb els alimentats amb la dieta n6.
- D'altra banda, aquest efecte sobre els AG precursors s'associà a una inhibició de la síntesi dels eicosanoides considerats procarcinogènics (PGE_2 i LTB_4) a la mucosa colònica amb les dietes n3 i n9, en comparació amb les dietes n6.

Aquesta modulació podria tenir un paper important en els mecanismes inhibitoris de la carcinogènesi colònica, el que caldrà demostrar en propers estudis.

ANNEX 1:

Composició vitamínica, mineral i d'elements traça per les tres dietes:

Vitamines	**Per 100 g de dieta**
Vitamina A (µg)	300
Vitamina D (µg)	6
Vitamina E (mg)	4
Vitamina C (mg)	73
Vitamina K (µg)	20
Tiamina (mg)	0,65
Riboflavina (mg)	0,7
Àcid nicotínic (mg)	8
Vitamina B_6 (mg)	0,94
Àcid fòlic (µg)	145
Vitamina B_{12} (µg)	1,6
Biotina (µg)	60
Àcid pantotènic (mg)	2,5
Colina (mg)	70
Inositol (mg)	32,5

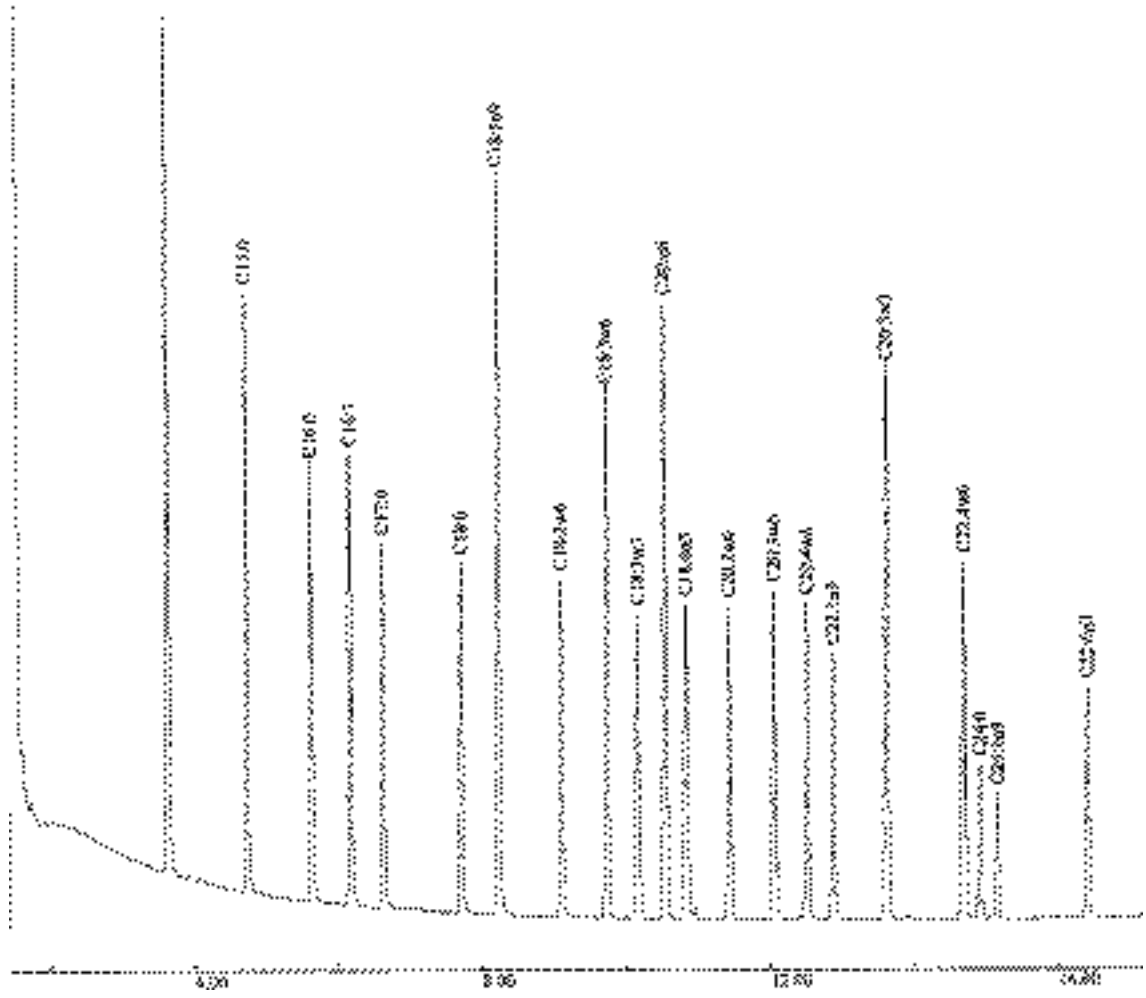
Minerals	**Per 100 g de dieta**
Sodi (mg)	270
Potassi (mg)	670
Clor (mg)	48
Calci (mg)	411
Fòsfor (mg)	597
Magnesi (mg)	86

Elements traça	**Per 100 g de dieta**
Ferro (mg)	38
Cobre (mg)	2,5
Zinc (mg)	30
Manganès (mg)	3,1
Iode (µg)	56
Molibdè (µg)	225
Seleni (µg)	90
Crom (µg)	75

Dades aportades per l'empresa suministradora de les dietes: Scientific Hospital Supplies International Ltd. (SHS); Liverpool, L7 9PT, England.

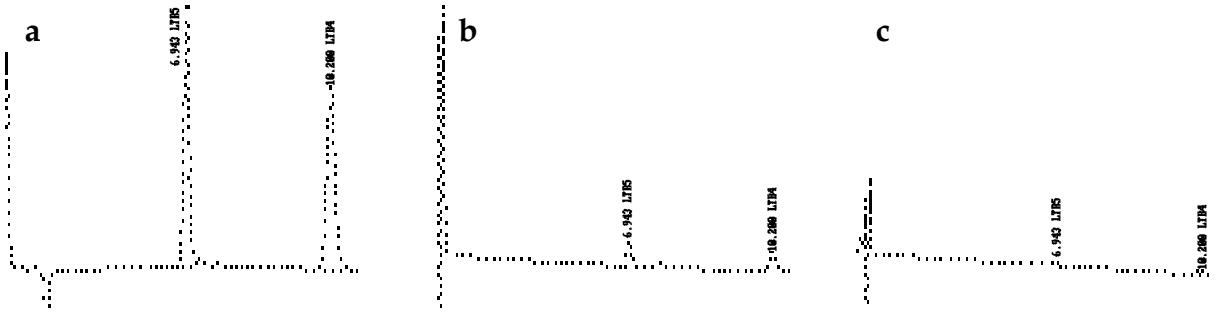
ANNEX 2.:

Estàndard extern utilitzat per identificar i quantificar els diferents AG de la mucosa colònica (Sigma Chemical, St Louis, Misouri, USA), així com la composició lipídica de les dietes, des de C15:0 a C24:0, mitjançant cromatografia gas-líquid (Perkin-Elmer Autosystem Chromatograp, Perkin-Elmer, Norwalk, CT) amb columna capil lar de 30 m x 0,25 mm i amb una fase estacionària SP 2330 (Teknocroma, Barcelona).

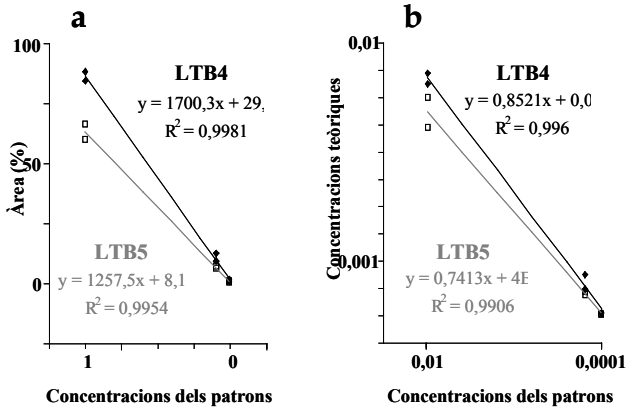


ANNEX 3:

I) Cromatogràmes obtinguts per HPLC i detectats per espectrofotometria (270 nm) on es mostren els temps de retenció del LTB_4 i del LTB_5 (10,2 min. i 6,9 min., respectivament), en les condicions metodològiques descrites a l'apartat **7.11.2** d'aquesta tesi, a partir de patrons no radioactius (Cayman Chemical Co.; Ann Arbor, U.S.A.). Les diferents concentracions emprades no modifiquen el temps de retenció (**a,** 1 µg/ml; **b**, 0,1 µg/ml; **c**, 0,01 µg/ml),, mentre que el límit de detecció s'establí per una concentració de 0,01µg/ml per ambdós isòmers.



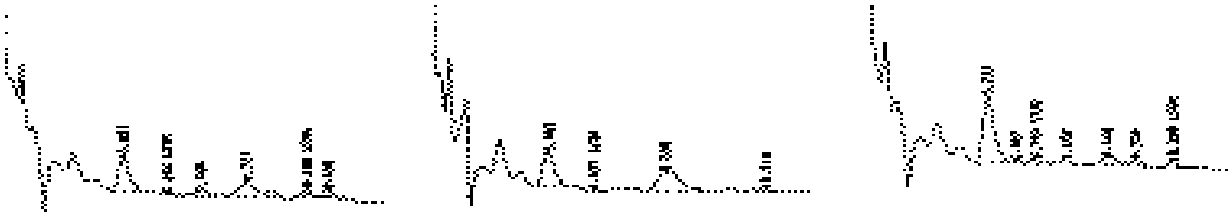
II) Coeficients de correlació linear obtinguts a partir de patrons no radioactius de LTB_4/B_5 (1, 0,1, 0,01 µg/ml) en relació a l'àrea dels pics detectats per HPLC + espectrofotometria (**a**); o a partir de patrons per sota del límit de detecció espectrofotomètrica (0,01, $1x10^{-3}$, $1x10^{-4}$ µg/ml) en relació a les concentracions esperades mitjançant HPLC+EIA (**b**).



III) Percentatge de recuperació dels leucotriens per la separació, mitjançant HPLC, d'una concentració de 1 µg/ml d'ambdós isòmers. Entre parèntesi es representa el coeficient de variació intraassaig (n=4).

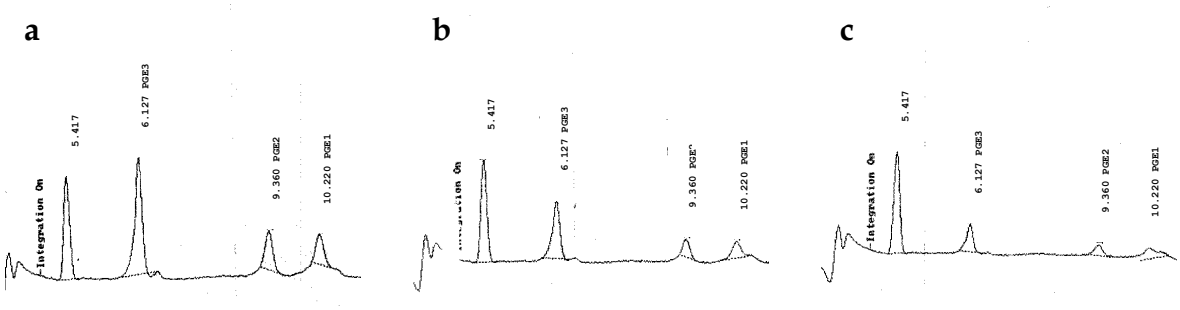
	LTB_4	LTB_5
Àrea esperada	2,78 (8,1%)	2,99 (4,12%)
Àrea calculada	2,96 (5,6 %)	2,64 (2,24 %)
Recuperació	107,8%	89,4%

IV) Exemples de cromatogràmes de dialitzats intracolònics on pot apreciar-se la baixa sensibilitat del procés HPLC+U.V. i, per tant, la necessitat de quantificar les concentracions de LTB_4/B_5 per EIA.



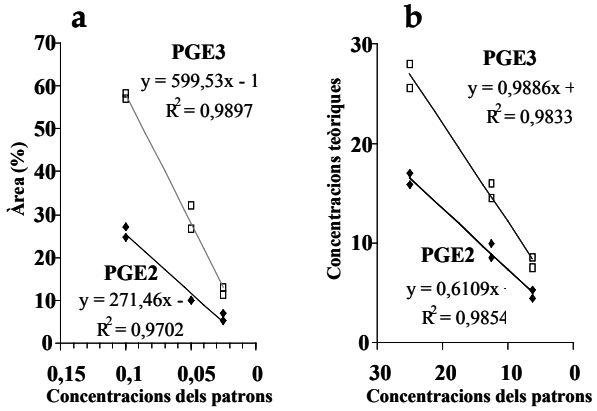
ANNEX 4:

I) Cromatogràmes obtinguts per HPLC amb detecció espectrofotomètrica (196 nm) que mostren els temps de retenció de patrons no radioactius de PGE_3, PGE_2 i PGE_1 (6,12 min., 9,36 min. i 10,22 min.; respectivament), segons les condicions metodològiques descrites a l'apartat **7.11.4** d'aquesta tesi. Els temps de retenció no foren alterats per la diferent concentració dels estàndards (**a,** 0,1 µg/ml; **b**, 0,05 µg/ml; **c**, 0,025 µg/ml), i el límit de detecció correspongué a la concentració de 0,025µg/ml pels tres isòmers prostaglandínics (**c**).



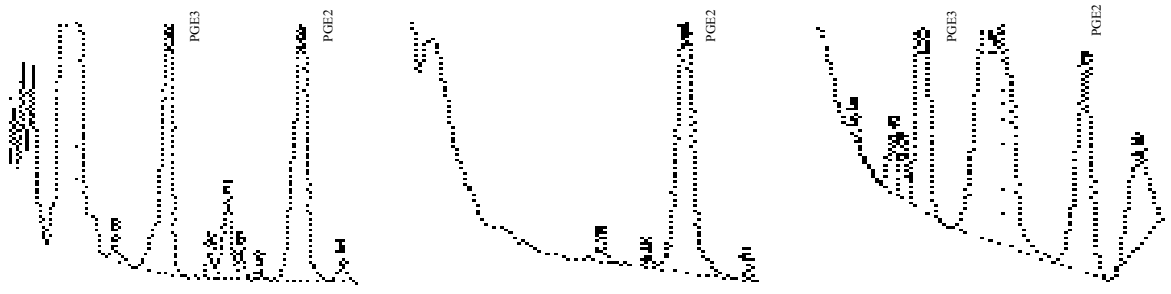
II) Coeficients de correlació linear obtinguts a partir de patrons no radioactius de PGE_2/E_3 (0,1, 0,05 i 0,025 µg/ml) en relació a l'àrea dels pics detectats per HPLC + espectrofotometria (**a**); o a partir de patrons per sota del límit de detecció espectrofotomètrica (0,025, $12{,}5x10^{-3}$, $6{,}25x10^{-3}$ µg/ml) en relació a les concentracions esperades mitjançant HPLC+EIA (**b**).

III) Percentatge de recuperació de la PGE_2 i la PGE_3 després de practicar la separació d'ambdós isomers mitjançant HPLC. L'assaig fou realitzat a una concentració de 0,1 µg/ml pels dos isòmers. Entre parèntesi es representa el coeficient de variació intraassaig (n=4).



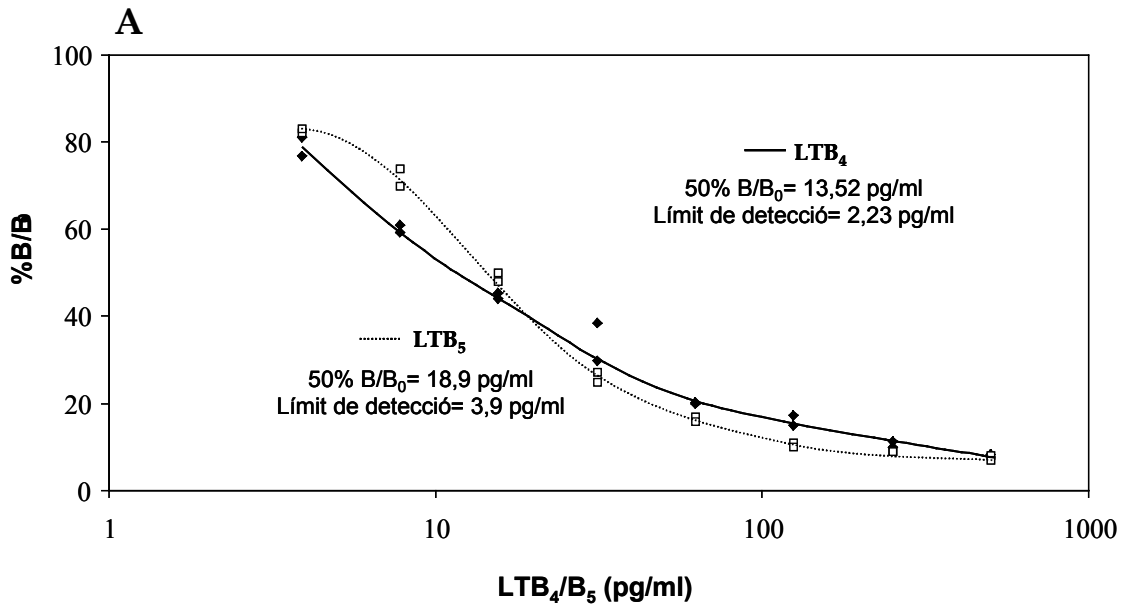
	PGE_2	PGE_3
Àrea esperada	2,58 (5,1%)	10,9 (3,86%)
Àrea calculada	2,13 (10,8%)	12,6 (13,7%)
Recuperació	82,56%	116%

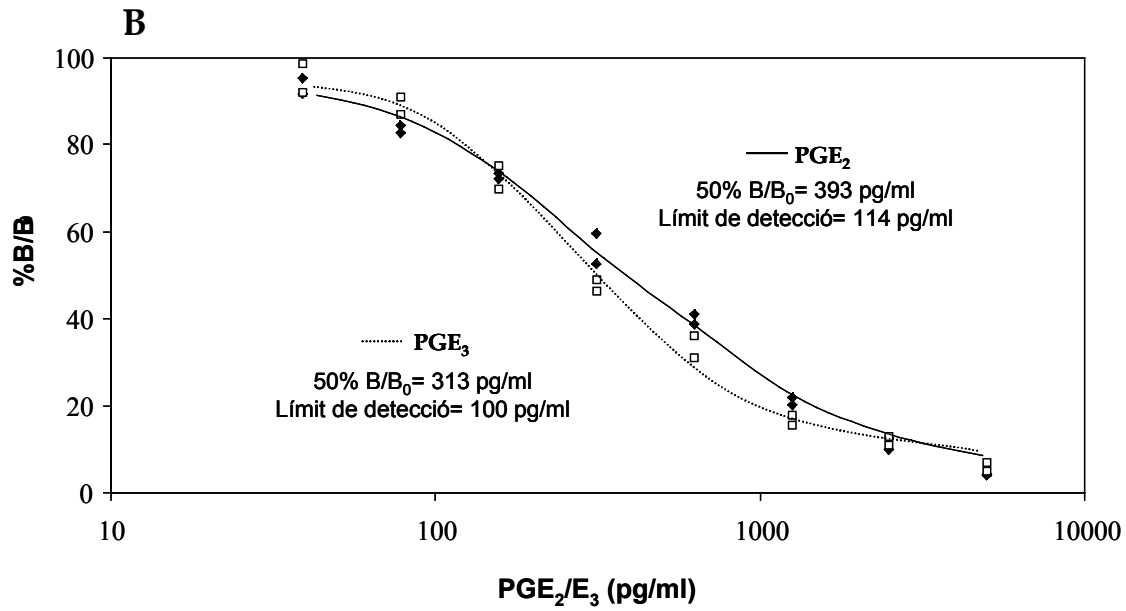
IV) Exemples de cromatogràmes (HPLC+U.V.) obtinguts a partir dels dialitzats intracolònics de les mostres problema. Un cop separades la PGE_2 i la PGE_3, les fraccions corresponents a cada isòmer prostaglandínic foren quantificades per EIA.



ANNEX 5:

Corves patró dels EIA realitzats pels LTB_4/B_5 (**A**)i per les PGE_2/E_3 (**B**). Com pot apreciar-se, la màxima linearitat s'obtè, aproximadament, al 80% central de la corba. La taxa $\%B/B_0$ expresa la relació entre l'absorvància d'una mostra (B) i l'absorvància deguda a la màxima quantitat de LT marcat que pot ser detectat sense la presència de LT lliure (B_0).





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