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◈종 설◈

프로스타글란딘 생합성 과정 및 천연물 유래의 COX-2 저해제

이화여자대학교 약학대학 약학과

박 은 정 · 이 상 국

Prostaglandin Biosynthesis and COX-2 Inhibitory Natural Products

Eun Jung Park and Sang Kook Lee

Department of Pharmacy, College of Pharmacy, Ewah Womans University, Seoul 120-750, Korea

Cancer incidence has continued to increase in recent years by environmental pollution, high fat diet, excessive stress, smoking as well as increasing life expectancy. Therefore, people have been more concerning about prevention of cancer. Especially, the concept of cancer chemoprevetion-the prevention, delaying or reversing cancer by intervention using nontoxic synthetic chemicals or chemicals from natural substances before malignancy-is the alternative way to conquer cancer. As far, the compounds that have cancer preventive effects are those which have antioxidant, anti-inflammatory and phase II enzyme inductive actions. This review will focus on inflammation-related enzymes and its products such as phospholipase A_2 (PLA_2), cyclooxygenase (COX) and prostaglandins (PGs). Based on recent results that some natural products have been shown cancer preventive effects, we also propose the agents that have COX-2 inhibitory activity. These potential inhibitory compounds will be promising therapeutic agents for prevention of cacner.

Key Words: Phospholipase A_2, Cyclooxygenase, Prostaglandin, Natural product

서 론

현대에는 영양환경의 개선, 의료기술의 발달로 인한 인간수명의 연장과 더불어 과도한 스트레스, 고지방식이, 환경오염, 흡연 등 생활방식 및 환경의 변화로 인해 암 발병률이 점진적으로 증가하고 있다. 우리나라도 예외는 아니어서, 국립암센터에서 발표한 2002년도 중앙암등록현황을 보면, 암 발생수는 전체 99,025건으로 2001년의 91,944건과 비교하여 7.7%가 증가하였다. 따라서 선택적으로 암세포를 사멸하는 항암제의 개발과 병행하여, 암의 발생을 억제하거나 혹은 생성된 암의 진행을 지연시키는 물질들을 발굴하여 적용하는 '화학적 암예방'에 대한 관심이 증대되고 있다. 화학적 암예방은 1976년 미국 국립암연구소의

책임저자 : 이상국 ㊞ 120-750, 서울특별시 서대문구 대현동 11-1, 이화여자대학교 약학대학
Tel: 02-3277-3023, Fax: 02-3277-2851, E-mail: sklee@ewha.ac.kr
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Michael Sporn 박사가 비타민 A 유도체의 암 발생 억제 현상을 보고하면서 도입된 개념으로 Michael Sporn 박사는 화학적 암예방을 '독성이 없는 합성 물질이나 천연물을 사용해 암이 생성되기 이전에 암을 예방하고, 이미 생성된 암의 악성화를 저해하는 것'이라고 정의하였다.[1] 현재까지 이러한 암 예방 효능이 있다고 알려진 물질들은 주로 항산화, 항염증, 제2단계 대사효소 유도 작용이 있으며, 특히 최근에는 항염증과 관련된 체내 프로스타글란딘(prostaglandin) 생합성 과정에 관여하는 효소 및 그 생성물의 암화에 미치는 영향에 대한 연구가 활발히 진행되고 있다. 따라서 본 논문에서는 프로스타글란딘 생합성 과정에 관여하는 효소인 phospholipase A_2 (PLA_2), cyclooxygenase (COX) 및 최종 산물인 프로스타노이드(prostanoid)의 역할에 대해 알아보고, 암화와의 연관성에 대해 기술하고자 한다. 또한, 2001년 타임지에서 견과류, 녹차, 마늘, 브로콜리, 블루베리, 적포도주, 토마토 등을 암예방 효과가 있는 식품으로 선정하였듯이, 수 천년을 거쳐 인류에 의해 안전성이 검증된 천연물 유래의 암예방제를 발굴하기 위한 연구들이 많이 진행되고 있는 바, 이와 관련하여 COX-2를 저해하는 효능을 지닌 천연물들에 대하여 살펴보고자 한다.

본 론

1) 개략적인 프로스타글란딘의 생합성 과정

세포막에 존재하는 인지질이 PLA_2에 의해 가수분해 되어 lysophospholipid 및 아라키돈산(arachidonic acid)을 생성하고, 생성된 아라키돈산은 다시 5-lipoxygenase를 통해 류코트리엔(leukotriene)들을 생성하거나 cyclooxygenase (COX)에 의해 프로스타노이드들을 생성한다. 최종 생성물인 류코드리엔들과 프로스타글란딘들은 각각의 수용체에 결합하여 천식, 염증반응, 암화, 통증 및 발열 등의 병리학적 과정에 관여한다.[2]

2) 아라키돈산 생성효소: Phospholipase A_2 (PLA_2: EC 3.1.1.4.)

대부분의 체내 아라키돈산은 음식물로부터 흡수된 리놀릭산이 간에서 전환되어 생성되는 것이며[3] 이후 acyltransferase와 transacylase에 의해 세포막 인지질과 결합된 상태로 존재하다가, 주로 PLA_2에 의해 인지질의 sn-2 위치가 가수분해 되면서 세포내로 분비된다. 또한 세포내 아라키돈산의 분비는 PLA_2 외에도 phospholipase C (PLC)-diacylglycerol (DAG) lipase 경로와 phospholipase D (PLD)-phosphatidic acid (PA) 경로를 거치기도 한다.[4,5] 포유류 PLA_2 효소는 크게 분비형-저분자 칼슘 의존성 PLA_2 (low-molecular- weight Ca^{2+}-dependent secretory phospholipase A_2: $sPLA_2$), 세포내-고분자 칼슘 의존성 PLA_2 (high- molecular-weight Ca^{2+}-dependent cytosolic phospholipase A_2: $cPLA_2$), 칼슘 비의존성 PLA_2 (Ca^{2+}-independent phospholipase A_2: $iPLA_2$)의 3가지 종류로 나뉜다.

그 중 $sPLA_2$는 약 14 kDa의 작은 분자로 아라키돈산에 대한 선택성이 없으며, 그룹 IB,[6,7] IIA,[8] IID,[9] IIE,[10] III,[11] V,[12] X,[13] XII[14] 등으로 분류된다. 그룹 IIA, IID, IIE, V 등은 Heparan sulfate proteoglycan (HSPG)-shuttling pathway에서, heparin과 결합한 후 GPI-anchored HSPG glypican과 함께 caveolae 혹은 raft를 형성하여 세포내로 함입되어 COX 근처에서 아라키돈산을 방출하고, 그룹 III, V, X 등은 주로 외세포막에 풍부한 phosphatidyl choline (PC)을 가수분해하여 아라키돈산을 생성한다.[15] $sPLA_2$와는 달리 $cPLA_2$는 sn-2 위치에 아라키돈산을 함유하는 인지질에 선택적성이 높으며 사이토카인, 호르몬, 신경전달물질, 미토겐, 항원, 내독소 등에 의해서 Ser-잔기가 mitogen-activated protein kinase (MAPK), Ca^{2+}/calmodulin-dependent protein kinase II 혹은 Mnk1에 의해 인산화되거나, 세포내 Ca^{2+}의 농도가 상승하면 활성화된다.[16] Ca^{2+}에 의해 활성화된 효소는 골지체, 소포체, 핵막 등으로 이동하여 작용하며 특히 $cPLA_{2\alpha}$는 lipopolysacchride (LPS), A23187, opsonized zymosan에 의한 초기 PGE_2 생성단계에 아라키돈산을 제공하는 동시에 COX-2를 유도하는 것으로 알려져 있다.[17~19] $iPLA_2$는 염증반응과 무관하며 세포막 인지질 항상성 유지에 중요한 역할을 한다. 그 외 각 PLA_2의 종류와 분포 및 분자량을 Table 1으로 정리하였다.

Table 1. PLA_2의 분류

그룹	발견조직(인간)	분자량(kDa)	유형
IB	이자	14.1	분비성
IIA	활액, 혈소판 심장 전립선, 소장, 대장	13.9	분비성
IID	이자, 비장	14.5	
IIE	두뇌, 심장, 폐, 태반	14.4	
IIIA	U937 세포/혈소판	85	분비성
IIIB	두뇌	100	
IIIC	심장, 근육	65	
IVA (cPLA2 α)	두루 존재	85	세포내
IVB (cPLA2 β)		114	
IVC (cPLA2 γ)		61	
IVD (cPLA2 δ)		55	
V	심장, 폐	13.6	분비성
VI	CHO 세포	80~85	Ca^{2+} 비의존성
VII	혈장	45	분비성
X	비장, 흉선, 말초혈관, 백혈구	13.7	분비성
XII	Th2 세포	18.7	분비성

3) 프로스타글란딘 생성효소: Cyclooxygenase

(1) COX의 종류: COX (EC1.14.99.1.)는 heme을 함유한 당단백(glycoprotein)으로 prostaglandin endoperoxide synthase, PG synthase, PGG/H synthase라고도 하며, 아라키돈산을 PGH_2로 전환하는 과정에 관여하는 효소이다. 현재까지 COX-1, -2, -3의 3가지 종류가 밝혀졌으며, COX-1 및 3는 일정하게 생성되는 효소(constitutive enzyme)인 반면, COX-2는 성장인자(EGF, PDGF, FGF), 신경전달물질, 염증유발인자(IL-1, TNF, INF, LPS, TPA), 산화적 스트레스, 외상, 호르몬(follicle-stimulating hormones, luteinizing hormone, estrogen), 암유전자(v-Src, v-Ras), 사이토카인, phorbol ester 등에 의해 유도되는 효소(inducible enzyme)이다(Table 2). 단, normal adult rat kidney, normal intact thyroid tissue에서 COX-2는 유도되지 않아도 일정한 발현을 보인다.[23~27]

(2) COX-2의 유전자 발현 조절: COX-2 유전자

Table 2. COX-1과 COX-2의 비교

	COX-1	COX-2
세포내 분포	Lumen of ER	ER and nuclear envelope
분자량	73 kDa	74 kDa
기 질	Only C_{20} carboxylic acids	C_{18} and C_{20} carboxylic acid
Locus	9q32~q33.3	1q25.2~q25.3

의 발현을 조절하는데 관여하는 promoter에는 NF-κB, NF-IL6 motif, CRE, E-box 등이 있으며, 유전자 발현을 저해하는 인자로는 peroxisome proliferator-activated receptor (PPAR) 리간드, glucocorticoid가 있다. PPAR은 CREB-binding protein(CBP)/p300과 결합하며 c-Jun의 발현을 저해하고, PPAR α는 NF-κB의 subunit인 p65/RelA와 p50의 발현을 저해하여 COX-2 유전자 발현을 저해하는 것

으로 알려져 있다. 한편, glucocorticoid는 glucocorticoid receptor (GR)와 복합체 형성 후 glucocorticoid response elements (GREs)를 경유해 항염증 유전자의 전사를 활성화 시켜 COX-2 유전자 발현을 저해한다.[28]

(3) 유전자 발현 후 조절: COX-2는 COX-24.8과 COX-22.8의 두 개의 이성체가 있으며, 그 차이는 3'-untranslated region (UTR)의 길이에 기인한다. 이 3'-UTR에 결합하는 단백질에는 AUF1, HuR, CPF-A, CUGBP2, TIAR, TIA-1 , TTP, hnRNP A0 등이 있으며, 그 가운데 TIA-1는 유전자 발현 후 조절에 중요한 역할을 하는 3'-UTR의 일부인 AU-rich element (ARE)에 결합하여 COX-2 발현을 저해하는 한편, HuR는 ARE와 결합하여 COX-2 발현을 안정화시킨다.[28~30]

4) 프로스타글란딘의 분비

COX에 의해 생성된 최종 산물인 PGG_2는 다시 prostacyclin synthase, isomerase, thromboxane synthase에 의해서 PGI_2, PGE_2, $PGF_{2\alpha}$, PGD_2, TXA_2 등을 생성한다. 이러한 프로스타노이드들은 자가분비(autocrine)-, 측분비(paracrine)-신호전달물질로 그 중 PGE_2는 세포막 투과능이 낮음에도 불구하고 수동적인 확산에 의해 세포 밖으로 분비되며, multi-drug resistance protein4 (MRP4)에 의해 분비되기도 한다.[31]

5) 프로스타글란딘의 불활성화

프로스타글란딘들은, 대부분의 포유류 조직에 존재하고 특히 폐, 신장과 태반에서 높은 활성을 보이는 세포질 내 효소인 NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH)에 의해 15(S)-hydroxyl 그룹이 15-keto 그룹으로 산화하여 불활성화된다.[32]

6) 각종 프로스타글란딘 및 그 수용체의 역할

PGG_2에서 생성된 프로스타글란딘들은 불안정하여, 쉽게 분해되며 자가분비 혹은 측분비 형식으로 rhodopsin-type G protein-coupled receptor인 프로스타노이드 수용체에 결합하여 생리학적 반응을 나타낸다.[46] 프로스타노이드 수용체는 기질인 프로스타글란딘의 유형에 따라 DP (DP_1, DP_2), EP (EP_1, EP_2, EP_3, EP_4), FP (FP_A, FP_B), IP, TP 등으로 나뉜다.[33]

(1) PGD_2 수용체[DP & $CRTH_2$ (DP_2)]: PGD_2는 활성화된 비만세포에서 주로 생성되는 프로스타노이드로, IgE를 매개로 하는 Type I 급성 알러지 반응를 개시하는 역할을 하는 것으로 알려져 있다. 이러한 PGD_2와 결합하는 수용체는 DP와 chemoattractant receptor-homologous molecule expressed on T helper type 2 cell ($CRHT_2$)의 두 종류가 있으며, PGD_2에 의한 혈소판 응집이 일어나기 위해서 cAMP가 필요하므로 DP의 분자생물학적 작용기전이 Gs protein→adenylate cyclase (AC)→cAMP→protein kinase A (PKA)로 이어지는 신호전달체계를 활성화시킨다는 가설이 있다. 하지만, 아직 입증되지는 않았고, 오히려 NIH-3T3 세포와 조골세포에서 Gq protein→phospholipase C (PLC)→protein kinase C (PKC) 신호전달체계를 활성화시킨다는 보고가 있다. 반면, $CRTH_2$는 Gi와 결합하여 cAMP를 낮춘다고 알려져 있다. 또한, 최근에는 PGD_2의 대사체인 15-deoxy-Δ(12,14)-prostaglandin J_2 (15-d(PGJ_2)가 peroxisome proliferator-activated receptor δ (PPAR δ)에 결합하여 염증관련 전사인자인 AP-1, STAT, NF-κB 등을 길항한다는 보고가 있다.[34] 이들 수용체의 경우, 마우스에서는 회장에서만 일반적으로 발현하고 그 외에 폐, 위 및 자궁에서는 아주 약하게 발현되며, 사람에서는 다른 프로스타노이드 수용체에 비해 가장 적게 존재하는 수용체로서 소장이나 뇌에서 소량 발현된다.[35,36]

(2) PGE_2 수용체(EP): EP_3와 EP_4는 EP_1이나 EP_2에 비해 PGE_2에 대한 친화도가 크며($Kd < 1$ nM)[37] EP_1이 신장, 폐, 위 등에 제한하여 발현되는 것에 비해 EP_3와 EP_4는 체내에서 두루 발현된다. EP_2는 EP 중에서 가장 적게 존재하지만 LPS 등과 같은 외부자극에 의해 발현이 유도된다.[38,39]

EP_1에 PGE_2가 결합하면 Gq→PLC→PKC 신호전달체계를 활성화시킨다.[40] 또한 EP_2에 PGE_2가 결합하면 Gs→AC→cAMP→protein kinase A (PKA) 신호전달체계가 활성화되고, 활성화된 PKA는 glycogen synthase kinase-3 (GSK-3)를 인산화시킨다. GSK-3가 인산화되면 β-catenin의 분해가 저해되며, 일부 β-catenin은 핵내로 들어가서 T-cell factor

(TCF)와 함께 전사인자로 작용한다.[40] 반면 EP_3에 PGE_2가 결합하면 Gi와 결합하여 cAMP 생성 저해 작용을 나타낸다. EP_4는 EP_2와는 달리 PGE_2와 결합하면 빠른 탈감작 및 내부함입이 일어나며 EP_4를 통해 활성화된 Gs는 순차적으로 phosphatidylinositol 3-kinase (PI3K)를 활성화시킨다. 활성화된 PI3K는 ERK를 활성화하고 뒤이어 early growth response factor-1 (EGR-1)이 유도된다. 유도된 EGR-1은 PGE_2 synthase (PGES), tumor necrosis factor-α (TNF-α), cyclin D_1의 발현을 조절하는 것으로 알려져 있다.[40] 또한 활성화된 PI3K는 PIP_2를 PIP_3로 전환하고 PIP_3는 PDK1을 활성화시켜 순차적으로 Akt를 인산화시키고 이는 다시 GSK3β를 인산화시켜서 β-catenin의 분해를 저해한다.[41]

(3) $PGF_{2\alpha}$ 수용체(FP): FP는 크게 FP_A와 FP_B 수용체로 나뉜다. 평소에 수용체 자체인 FP_B는 PI3K와 결합하여 이를 활성화시켜 E-cadherin과 β-catenin을 세포내로 들여보낸다. 대부분의 세포질내 β-catenin은 glycogen synthase kinase (GSK)에 의해 인산화되어 ubiquitin-mediated degradation을 일으킨다. $PGF_{2\alpha}$가 결합하면 p125 focal adhesion kinase (FAK)의 tyrosine 잔기를 인산화시키는 Rho와 PKC가 활성화되고, 세포질내 β- catenin의 인산화가 지연되어 핵내로 들어가는 β- catenin이 증가한다. 핵내 β-catenin은 TCF와 결합 후 COX-2 등의 promoter에 붙어 발현을 증가시킨다.[41] FP는 corpus luteum에서 주로 발현되며 마우스 kidney의 cortical tubule과 stomach gland, NIH 3T3 fibroblastic cell line에서도 발견되었다.[42,43]

(4) PGI_2 수용체(IP): IP는 dorsal root ganglion (DRG)의 neuron에서 가장 풍부하게 발견되며 megakaryocyte이나 동맥평활근에서도 과발현되고 통증과 관련이 있는 것으로 추정된다.[44]

(5) TXA_2 수용체(TP): TPα, TPβ의 두 가지 형태가 있다. TP는 TxA_2가 결합하면 Gq→PLC→PKC 신호전달체계를 활성화 시킨다. TP는 대부분의 조직에 존재하며 폐, 신장, 심장에 존재하는 혈관에 풍부할 뿐 아니라, 흉선(thymus), 비장(spleen) 등에서 주로 발현된다.[45~47]

7) 암화와의 관련성

(1) COX와 암화(carcinogenesis): COX-2는 pre-malignant 및 malignant tissue에 주로 과발현되는 것으로 알려져 있다. 유선에 인간 *COX-2*를 과발현 되도록 조작한 multiparous female transgenic mice는 focal mammary gland hyperplasia, dysplasia, metastatic tumor를 만들었고, 피부에 COX-2를 과발현하도록 조작한 transgenic mice는 epidermal hyperplasia와 dysplasia를 유발하였다. 또한 COX-2를 knock-out시킨 쥐에서 intestinal tumor와 skin papilloma의 진행이 크게 줄었으며, COX-2 선택적 저해제가 동물모델에서 소장암, 식도암, 설암, 유방암, 피부암, 폐암, 방광암의 생성이 저해되었다.[48~68]

최근에는 COX-2뿐 아니라 COX-1이 발암과정에 관여한다는 논문들이 보고되고 있다. 인간 난소암, 전립선암, 유방암, 자궁암, 쥐 폐암 조직에서 COX-1의 과발현이 보고된 바 있으며, COX-1의 유전자발현 저해시 Min mice에서의 소장암생성 억제, COX-1 knockout 시 쥐의 피부암화 감소, COX-1 선택적 저해제의 유방암모델 쥐에서 전이 억제, 난소암에서 AGF의 생성 증가가 확인된 바 있다.[69~77]

(2) PLA_2와 암화: $sPLA_2$-IIA가 암 발생과 진행에 중요한 역할을 한다는 보고가 있으며, familial adenomatous polyposis (FAP)로부터 colorectal adenomas가 생성된 환자의 조직에서 $sPLA_2$-IIA의 단백질과 유전자 발현이 모두 상승해 있음을 확인하였다.[20~22] 또한 대장, 소장, 폐의 암조직에서 $cPLA_{2\alpha}$의 발현이 상승되어 있음이 보고되었다.[36~39]

(3) 프로스타노이드 및 EP와 암화: 최근 프로스타노이드 및 EP의 암화에 대한 연관성을 밝힌 논문이 많이 보고되고 있다. 실제로 EP_1 수용체 knock-out 쥐에서 azoxymethane-induced aberrant crypt foci 생성 저해,[81] EP_2 수용체 knock-out Apc (Δ716)mice에서 소장용종의 수와 혈관신생의 강도 및 VEGF의 발현 감소, EP_2 수용체 knock-out mice에서 암관련 면역결핍과 불완전한 수지상 세포의 분화가 보고되었고[82,83] EP_3 수용체 knock-out 쥐에서 혈관신생 및 암성장의 감소, IP와 결합하는 PGI_2 유도체의 전이 억제 등이 밝혀졌다.[84,85] 최근에는 대장암과 EP_4의 상관성에 대한 연구도 활발히 이루어지고 있는데 EP_4 knock-out 쥐에서 azoxymethane을 주입하여 생성되는 aberrant crypt

foci (ACF)의 저해, EP_4 수용체 길항제 처리시 Min mouse에서의 소장용종의 수 증가, colorectal carcinoma cell에서 세포 이동성과 증식 증가, 담낭의 암조직에서 EP_4의 발현 등이 보고된 바 있다.[78~80]

8) 천연물 유래의 COX-2 저해활성물질

천연물에서 유래한 암예방물질로 생강, 마늘, 콩, 울금, 양파, 토마토, 십자화과 식물들, 고추, 녹차 등이 알려져 있다. 실제로 위의 식품들을 빈번하게 섭취하는 동남아의 인도와 그렇지 않은 미국의 암발생률 비교시 대장, 위, 전립선, 유방 외 다른 암들의 발생빈도가 상대적으로 낮다는 보고도 있다.[90] 이렇듯 천연물 유래의 물질들 중 암예방 효과를 가지고 있는 것이 많고 현재 활발히 연구가 진행되고 있으므로 천연물 유래 물질 중 COX-2 저해활성이 있는 물질을 중심으로 정리해 보았다(Table 3~6).

Table 3. COX-2 효소 활성을 저해하는 물질들

Origin	Compound	References
Allium sativum	Ajoene	Dirsch & Wollmar (1998)[91]
Aloe vera	Aqueous Extract	Vazquez et al. (1996)[92]
Atuna racemosa Raf. Ssp. Racemosa	4'-MeO-(-)-gallocatechin	Noreen et al. (1998)[93]
BalatonTM tart cherries	Cyanidin	Wang et al. (1999)[94]
Bidens pilosa	EtOH Extract	Jager et al. (1996)[95]
Ceiba pentandra Gaertner	(+)-Catechin Vavain Vavain-3'-O-β-glucoside	Noreen et al. (1998)[96]
Cryptocarya wyliei	–	Zschocke et al. (2000)[97]
Endospermum diadenum	Akendo 3	Pay et al. (1996)[98]
Epilobium angustifolium L.	Myricetin-3-O-β-D-glucuronide	Hiermann et al. (1998)[99]
Eucomis autumnalis	EtOH Extract	Jager et al. (1996)[95]
Garcinia mangostana L.	Mangostin	Nakatani et al. (2002)[100]
Harpephyllum caffrum	EtOH Extract	Jager et al. (1996)[95]
Helichrysum nudifolium	EtOH Extract	Jager et al. (1996)[95]
Honeybee propolis	Caffeic acid phenethyl ester	Michaluart et al. (1999)[101]
Leonotis intermedia	EtOH Extract	Jager et al. (1996)[95]
Leonotis leonorus	EtOH Extract	Jager et al. (1996)[95]
Melampodium leucanthum	Leucanthin B	Hwang et al. (1996)[102]
Ocimum sanctum Linn	Eugenol	Kelm MA et al. (2000)[103]
Ocotea bullata	EtOH Extract	Jager et al. (1996)[95]
Plantago major L.	Ursolic acid	Ringbom et al. (1998)[104]
Rumex saggitatus	EtOH Extract	Jager et al. (1996)[95]
Scutellaria baicalensis	Wogonin	Wakabayashi et al. (2000)[105]
Solanum mauritianum	EtOH Extract	Jager et al. (1996)[95]
Stephania tetrandrae S. Moore	fangchinoline	Choi et al. (2000)[106]
Synadenium cupulare	EtOH Extract	Jager et al. (1996)[95]
Trichilia dregeana	EtOH Extract	Jager et al. (1996)[95]
Vantanea peruviana Macbr.	Ouratea-pro-anthocyanidin	Noreen et al. (1998)[107]
Common in plants	Oleanolic acid	Ringbom et al. (1998)[104]
	γ-Tocopherol	Qing Jiang et al. (2000)[108]

Table 4. 프로스타노이드 생성 저해 물질들

Origin	Compound	References
Acacia rehmanniana	Aqueous extract	McGaw et al. (1998)[109]
Achanthella auratiaca	Hymenialdisine	Roshak et al. (1997)[110]
Allium sativum	Ajoene	Dirsch & Wollmar (1998)[91]
	Allicin	
Alpinia officinarum Hance	Pinocembrin	
	galangin 3-methyl ether, galangin	
	kaempferid	
	5-hydroxy-7-(4''-hydroxy-3''-meth-oxyphenyl)-1-phenyl-3-heptanone	
Ambrosia confertiflora	Confertiflorin	Hwang et al. (1996)[102]
Artemisia absinthium	5,6,3',5'-tetramethoxy-7,4'-hydrox yflavone(p7F)	Lee et al. (2004)[111]
Astragalus membranaceus	7, 2'-Dihydroxy-3',4'-dimethoxyiso flavan-7-O-β-D-glucoside	Kim et al. (2001)[112]
	Calycosin-7-O-β-D-glucoside	
Belamacanda chinensis	Tectoridin	Kim et al. (1999)[113]
Belamacanda chinensis	Tectorigenin	Kim et al. (1999)[113]
	Resveratrol	Subbaramaiah et al. (1998)[114]
Cacospongia mollior	Scalaradial	Glaser & Lock (1995)[115]
Cryptocarya latifolia	Aqueous extracts	Zschocke et al. (2000)[97]
Curcuma longa L.	Curcumin	Zhang et al. (1999)[116]
Dalbergia odorifera	Cinnamylphenol,	Goda Y et al. (1992)[117]
	isoflavene, benzoic acid derivative	
Encelia farinosa	Encelin	Hwang et al. (1996)[102]
Enhydra fluctuans	Enhydrin	Hwang et al. (1996)[102]
Eugenia caryophyllata Thunberg	Egenol	Kim et al. (2003)[118]
Fish liver oil	Cholecalciferol	Kanekura et al. (1998)[119]
Garcinia mangostana L.	mangosteen	Nakatani et al. (2002)[120]
Helenium tenuifolium	Tenulin	Hwang et al. (1996)[102]
Helenium elegans		
Honeybee propolis	Caffeic acid phenethyl ester	Michaluart et al. (1999)[101]
Luffariella variabilis	Manoalide	Glaser & Lock (1995)[115]
Melampodium leucanthum	Leucanthin B	Hwang et al. (1996)[102]
	Melampodin A	
Scutellaria baicalensis	Oroxylin A	Chen et al. (2000)[121]
Scutellaria baicalensis	wogonin	Wakabayashi et al. (2000)[105]
Stephania tetrandria	Tetrandrine	Pang & Hoult (1997)[122]
Tanacetum parthenium	Parthenolide	Hwang et al. (1996)[102]
Tripterygum wilfordii Hook F	Triptolide	Tao et al. (1998)[123]
Zingiber zerumbet Smith	Zerumbone	Murakami A. et al. (2002)[124]
Common in plants	Costunolide	Hwang et al. (1996)[102]
	Burrodin	
	Psilostachyin A	
	All-trans-retinoic acid	Mestre et al. (1997)[126]
	13-cis-retinoic acid	
	Retinyl acetate	
	γ-Tocopherol	Qing Jiang et al. (2000)[127]

Table 5. COX-2 단백질 발현 저해 물질들

Origin	Compound	References
Acacia victoriae	Avicin G	Valsala Haridas et al. (2001)[128]
Scutellaria baicalensis	Wogonin	Wakabayashi et al. (2000)[105]
Eugenia caryophyllata Thunberg	Eugenol	Kim et al. (2003)[118]
Green tea	(-)Epigallocatechin-3-gallate (EGCG)	Hussain et al. (2005)[129]

Table 6. COX-2 유전자 발현 저해 물질들

Origin	Compound	References
Artemisia absinthium.	5,6,3',5'-tetramethoxy-7,4'-hydroxyflavone (p7F)	Lee et al. (2004)[111]
Axinella verrucosa	Hymenialdisine	Roshak et al. (1997)[130]
Belamacanda chinensis	Tectoridin	Kim et al. (1999)[131]
Belamacanda chinensis	Tectorigenin	Kim et al. (1999)[131]
Cacospongia mollior	Scalaradial	Glaser & Lock (1995)[115]
Cassia quinquangulata Rich.	Resveratrol	Subbaramaiah et al. (1998)[114]
Citrus depressa	Nobiletin	Tanaka et al. (2004)[132]
Curcuma longa L.	Curcumin	Zhang et al. (1999)[116]
Eugenia caryophyllata Thunberg	Eugenol	Kim et al. (2003)[118]
Fungus strain KF9	Radicicol	Chanmungam et al. (1995)[133]
genera Berberis and Coptis	Berberine	Fukuda et al. (1999)[134]
Green tea	(-)epigallocatechin-3-gallate (EGCG)	Hussain et al. (2005)[129]
Honeybee propolis	Caffeic acid phenethyl ester	Michaluart et al. (1999)[101]
Magnolia grandiflora	Parthenolide	Hwang et al. (1996)[102]
Scutellaria baicalensis	Wogonin	Chen et al. (2001)[125]
Stephania tetrandira	Tetrandrine	Pang & Hoult (1997)[122]
Tripterigum wilfordii Hook F	Triptolide	Pang & Hoult (1997)[122]
widespread in fruits and vegetables of red-blue color	Anthocyanin	Hou et al. (2004)[135]
Zingiber zerumbet	Zerumbone	Tanaka T. et al. (2001)[136]
Common in plants	Genistein	Chanmugam et al. (1995)[133]
	Naringenin	Raso et al. (2001)[137]
	Herbimycin A	Chanmugam et al. (1995)[133]
	All-trans-Retinoic acid	Mestre et al. (1997)[126]
	13-cis-Retinoid acid	
	Retinyl acetate	

결 론

암은 현대인의 건강을 위협하는 최대의 적으로서, 최근 우리나라 사망원인 1순위의 질병이다. 그러나 지난 수십 년간 암을 치료하기 위해 약물요법을 비롯하여 방사선 요법, 수술 요법 등을 개발하였음에도 불구하고 암으로 인한 사망률은 줄

어들지 않고 있다. 따라서, 암이 생성되기 이전에 암을 예방하려는 화학적 암예방이 경제적이고 효율적인 접근 방법으로 인식되고 있으며, 그 중에서 염증 반응을 매개하는 과정에 관여하는 효소 및 생성물에 대한 관심이 증가하고 있다. 특히 천연물에서 유래된 물질들의 COX-2 활성에 미치는 영향에 대한 연구가 많이 진행되고 있으며, 이러한 연구들이 새로운 암예방제를 개발하는데 기여할 것으로 사료된다.

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Modulation of Apoptosis-related Signal Transduction by Celecoxib, a Selective COX-2 Inhibitor in Comparison with Estrogen in Perimenopausal Mammary Glands

Tae-Kyung Kim, In-Ja Park and Ock Jin Park

Department of Food and Nutrition, Hannam University, Daejeon 306-791, Korea

This investigation was intended to study the expression of cyclooxygenase-2 (COX-2) and mapkinase, and apoptosis related gene expression in normal mammary glands of perimenopausal female rats fed oral celecoxib, a selective COX-2 inhibitor and estrogen. The expression of pERK1/2 showed the similar patterns as COX-2 by the oral treatment of celecoxib and estrogen. It was found that celecoxib induced up-regulation of bcl-2 in mammary gland buds. The regulation of bax was decreased in celecoxib supplemented rats. The bcl-2/bax ratio was higher in celecoxib supplemented rats. However, bcl-2/bax ratio was highest in celecoxib group. The up-regulation of COX-2 was observed in celecoxib in mammary gland buds. The similar trend was not displayed with mapkinase expression. Compared to estrogen feeding, bcl-2 expression was upregulated in celecoxib and down-regulating effect was observed with bax expression. The up-regulation of bcl-2 was accompanied by the decreased expression of COX-2. The oral administration of celecoxib caused significant reduction in bcl-2/bax ratio compared to the control indicating that there might be more apoptotic activity in celecoxib treatment. However, estrogen, a known stimulator of cell proliferation also showed the apoptotic potential compared to control or celecoxib. The increased apoptotic potential by celecoxib or estrogen resulted from the different patterns in bcl-2 or bax regulation. The lowering of bcl-2/bax ratio by celecoxib was resulted from the increased expression of bas, while the reduction of bcl-2/bax observed with estrogen was from the decreased bcl-2 and the increased bax. These findings suggest that both bcl-2 and bax are involved in the apoptotic control of celecoxib, and bcl-2 is a significant factor in apoptotic control of estrogen.

Key Words: Celecoxib, COX-2, Molecular markers related to apoptosis, Perimenopausal female rat, Mammary gland buds

Corresponding author : Ock Jin Park, Department of Food and Nutrition, Hannam University, 133 Ojeong-dong, Daedeok-gu, Daejeon 306-791, Korea. Tel: +82-42-629-7493, Fax: +82-42-629-7490, E-mail: ojpark@hannam.ac.kr
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