Blockade of nuclear factor-?B signaling pathway and anti-inflammatory activity of cardamomin, a chalcone analog from Alpinia conchigera

Lee J.-H., Haeng S.J., Phan M.G., Jin X., Lee S., Phan T.S., Lee D., Hong Y.-S., Lee K., Jung J.L.

Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea; Laboratory of Immune Modulator, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea; Faculty of Chemistry, Vietnam National University, Hanoi, Viet Nam; Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, P.O. Box 115, Yuseong, Daejeon 305-600, South Korea

Abstract: Nuclear factor-?B (NF-?B) and the signaling pathways that regulate its activity have become a focal point for intense drug discovery and development efforts. NF-?B regulates the transcription of a large number of genes, particularly those involved in immune, inflammatory, and antiapoptotic responses. In our search for NF-?B inhibitors from natural resources, we identified cardamomin, 2?,4?-dihydroxy-6?-methoxychalcone, as an inhibitor of NF-?B activation from Alpinia conchigera Griff (Zingiberaceae). In present study, we demonstrated the effect of cardamomin on NF-?B activation in lipopolysaccharide (LPS)-stimulated RAW264.7 cells and LPS-induced mortality. This compound significantly inhibited the induced expression of NF-?B reporter gene by LPS or tumor necrosis factor (TNF)-? in a dose-dependent manner. LPS-induced production of TNF-? and NO as well as expression of inducible nitric-oxide synthase and cyclooxygenase-2 was significantly suppressed by the treatment of cardamomin in RAW264.7 cells. Also, cardamomin inhibited not only LPS-induced degradation and phosphorylation of inhibitor ?B? (I?B?) but also activation of inhibitor ?B (I?B) kinases and nuclear translocation of NF-?B. Further analyses revealed that cardamomin did not directly inhibit I?B kinases, but it significantly suppressed LPS-induced activation of Akt. Moreover, cardamomin suppressed transcriptional activity and phosphorylation of Ser536 of RelA/p65 subunit of NF-?B. However, this compound did not inhibit LPS-induced activation of extracellular signal-regulated kinase and stress-activated protein kinase/c-Jun NH_2-terminal kinase, but significantly impaired activation of p38 mitogen-activated protein kinase. We also demonstrated that pretreatment of cardamomin rescued C57BL/6 mice from LPS-induced mortality in conjunction with decreased serum level of TNF-?. Together, cardamomin could be valuable candidate for the intervention of NF-?B-dependent pathological condition such as inflammation. Copyright ?? 2006 by The American Society for Pharmacology and Experimental Therapeutics.

Index Keywords: 2',4' dihydroxy 6' methoxychalcone; antiinflammatory agent; chalcone derivative; cyclooxygenase 2; I kappa B; immunoglobulin enhancer binding protein; inducible nitric oxide synthase; lipopolysaccharide; mitogen activated protein kinase; mitogen activated protein kinase p38; nitric oxide; protein kinase B; serine; stress activated protein kinase; tumor necrosis factor alpha; unclassified drug; Alpinia; Alpinia conchigera; animal cell; animal experiment; antiinflammatory activity; article; cell death; controlled study; cytokine production; drug effect; drug efficacy; drug mechanism; enzyme inactivation; gene expression regulation; human; human cell; inhibition kinetics; male; mouse; nonhuman;

pharmacogenetics; priority journal; protein phosphorylation; reporter gene; signal transduction; transcription regulation; Alpinia; Animals; Anti-Inflammatory Agents; Blotting, Western; Cell Survival; Chalcones; Cyclooxygenase 2 Inhibitors; Electrophoretic Mobility Shift Assay; Enzyme Inhibitors; Humans; I-kappa B Proteins; Lipopolysaccharides; Luciferases; Macrophages; Mice; Mice, Inbred C57BL; NF-kappa B; Nitric Oxide Synthase Type II; Oncogene Protein p65(gag-jun); Phosphorylation; Plasmids; Signal Transduction; Trans-Activation (Genetics); Tumor Necrosis Factor-alpha

Year: 2006
Source title: Journal of Pharmacology and Experimental Therapeutics
Volume: 316
Issue: 1
Page : 271-278
Cited by: 24
Link: Scorpus Link
Chemicals/CAS: inducible nitric oxide synthase, 501433-35-8; mitogen activated protein kinase, 142243-02-5; nitric oxide, 10102-43-9; protein kinase B, 148640-14-6; serine, 56-45-1, 6898-95-9; stress activated protein kinase, 155215-87-5; Anti-Inflammatory Agents; cardamonin; Chalcones; Cyclooxygenase 2 Inhibitors; Enzyme Inhibitors; I-kappa B Proteins; Lipopolysaccharides; Luciferases, EC 1.13.12.-; NF-kappa B; Nitric Oxide Synthase Type II, EC 1.14.13.39; Oncogene Protein p65(gag-jun); Tumor Necrosis Factor-alpha
Correspondence Address: Jung, J.L.; Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, P.O. Box 115, Yuseong, Daejeon 305-600, South Korea; email: jjlee@kribb.re.kr
ISSN: 223565
CODEN: JPETA
DOI: 10.1124/jpet.105.092486
PubMed ID: 16183703
Language of Original Document: English
Abbreviated Source Title: Journal of Pharmacology and Experimental Therapeutics
Document Type: Article
Source: Scopus
Authors with affiliations:

1. Lee, J.-H., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea
2. Haeng, S.J., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea
3. Phan, M.G., Faculty of Chemistry, Vietnam National University, Hanoi, Viet Nam
4. Jin, X., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea
5. Lee, S., Laboratory of Immune Modulator, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea
6. Phan, T.S., Faculty of Chemistry, Vietnam National University, Hanoi, Viet Nam
7. Lee, D., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea

8. Hong, Y.-S., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea
9. Lee, K., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea
10. Jung, J.L., Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea, Anticancer Research Laboratory, Korea Research Institute of Bioscience and Biotechnology, P.O. Box 115, Yuseong, Daejeon 305-600, South Korea

References:

1. Baeuerle, P.A., Baltimore, D., A 65-kD subunit of active NF-?B is required for inhibition of NF-?B by I?B (1989) Genes Dev, 3, pp. 1689-1698
2. Baldwin Jr., A.S., The NF-?B and I?B proteins: New discoveries and insights (1996) Annu Rev Immunol, 14, pp. 649-683
3. Ballard, D.W., Dixon, E.P., Peffer, N.J., Bogerd, H., Doerre, S., Stein, B., Greene, W.C., The 65-kDa subunit of human NF-?B functions as a potent transcriptional activator and a target for v-Rel-mediated repression (1992) Proc Natl Acad Sci USA, 89, pp. 1875-1879
4. Ban, H.S., Suzuki, K., Lim, S.S., Jung, S.H., Lee, S., Ji, J., Lee, H.S., Ohuchi, K., Inhibition of lipopolysaccharide-induced expression of inducible nitric oxide synthase and tumor necrosis factor-alpha by 2?-hydroxychalcone derivatives in RAW 264.7 cells (2004) Biochem Pharmacol, 67, pp. 1549-1557
5. DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E., Karin, M., A cytokine-responsive I?B kinase that activates the transcription factor NF-?B (1997) Nature (Lond), 388, pp. 548-554
6. Ghosh, S., Karin, M., Missing pieces in the NF-?B puzzle (2002) Cell, 109, pp. S81-S96
7. Ghosh, S., May, M.J., Kopp, E.B., NF-?B and Rel proteins: Evolutionarily conserved mediators of immune responses (1998) Annu Rev Immunol, 16, pp. 225-260
8. Giri, S., Rattan, R., Singh, A.K., Singh, I., The 15-deoxy-??12,14-prostaglandin J2 inhibits the inflammatory response in primary rat astrocytes via down-regulating multiple steps in phosphatidylinositol 3-kinase-Akt-NF-?B-p300 pathway independent of peroxisome proliferator-activated receptor ?? (2004) J Immunol, 173, pp. 5196-5208
9. Gustin, J.A., Ozes, O.N., Akca, H., Pincheira, R., Mayo, L.D., Li, Q., Guzman, J.R., Donner, D.B., Cell type-specific expression of the I?B kinases determines the significance of phosphatidylinositol 3-kinase/Akt signaling to NF-?B activation (2004) J Biol Chem, 279, pp. 1615-1620
10. Henkel, T., Zabel, U., Van Zee, K., M?ller, J.M., Fanning, E., Baeuerle, P.A., Intramolecular masking of the nuclear location signal and dimerization domain in the precursor for the p50 NF-?B subunit (1992) Cell, 68, pp. 1121-1133
11. Itokawa, H., Morita, M., Mihashi, S., Phenolic compounds from the rhizomes of Alpinia speciosa (1981) Phytochemistry, 20, pp. 2503-2506
12. Jhun, B.S., Jin, Q., Oh, Y.T., Kim, S.S., Kong, Y., Cho, Y.H., Ha, J., Kang, I., 5-Aminoimidazole-4-carboxamide riboside suppresses lipopolysaccharide- induced TNF-alpha production through inhibition of phosphatidylinositol 3-kinase/Akt activation in RAW264.7 murine macrophages (2004) Biochem Biophys Res Commun, 318, pp. 372-380
13. Koide, N., Sugiyama, T., Mori, I., Mu, M.M., Yoshida, T., Yokochi, T., C2-Ceramide inhibits LPS-induced nitric oxide production in RAW264.7 macrophage cells through down-regulating the activation of Akt (2003) J Endotoxin Res, 9, pp. 85-90
14. Koul, D., Yao, Y., Abbruzzese, J.L., Yung, W.K., Reddy, S.A., Tumor suppressor MMAC/PTEN inhibits cytokine-induced NF-?B activation without interfering with the I?B degradation pathway (2001) J Biol Chem, 276, pp. 11402-11408
15. Lee, J.H., Hwang, B.Y., Kim, K.S., Nam, J.B., Hong, Y.S., Lee, J.J., Suppression of RelA/p65 transactivation activity by a lignoid manassantin isolated from Saururus chinensis (2004) Biochem Pharmacol, 66, pp. 1925-1933

16. Lee, J.H., Koo, T.H., Hwang, B.Y., Lee, J.J., Kaurane diterpene, kamebakaurin, inhibits NF-?B by directly targeting the DNA-binding activity of p50 and blocks the expression of antiapoptotic NF-?B target genes (2002) J Biol Chem, 277, pp. 18411-18420
17. Lu, Y., Wahl, L.M., Production of matrix metalloproteinase-9 by activated human monocytes involves a phosphatidylinositol-3 kinase/Akt/IKK?/NF-?B pathway (2005) J Leukoc Biol, 78, pp. 1-7
18. Madan, B., Batra, S., Ghosh, B., 2?-Hydroxychalcone inhibits nuclear factor-?B and blocks tumor necrosis factor-?- and lipopolysaccharide-induced adhesion of neutrophils to human umbilical vein endothelial cells (2000) Mol Pharmacol, 58, pp. 526-534
19. Madrid, L.V., Mayo, M.W., Reuther, J.Y., Baldwin Jr., A.S., Akt stimulates the transactivation potential of the RelA/p65 subunit of NF-?B through utilization of the I?B kinase and activation of the mitogen-activated protein kinase p38 (2001) J Biol Chem, 276, pp. 18934-18940
20. Madrid, L.V., Wang, C.Y., Guttridge, D.C., Schottelius, A.J., Baldwin Jr., A.S., Mayo, M.W., Akt suppresses apoptosis by stimulating the transactivation potential of the RelA/p65 subunit of NF-?B (2000) Mol Cell Biol, 20, pp. 1626-1638
21. Mayo, M.W., Madrid, L.V., Westerheide, S.D., Jones, D.R., Yuan, X.J., Baldwin Jr., A.S., Whang, Y.E., PTEN blocks tumor necrosis factor-induced NF-?B-dependent transcription by inhibiting the transactivation potential of the p65 subunit (2002) J Biol Chem, 277, pp. 11116-11125
22. Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Manning, A., IKK-1 and IKK-2: Cytokine-activated I?B kinases essential for NF-?B activation (1997) Science (Wash DC), 278, pp. 860-865
23. Nakano, H., Shindo, M., Sakon, S., Nishinaka, S., Mihara, M., Yagita, H., Okumura, K., Differential regulation of I?B kinase ? and ? by two upstream kinases, NF-?B-inducing kinase and mitogen-activated protein kinase/ERK kinase kinase-1 (1998) Proc Natl Acad Sci USA, 95, pp. 3537-3542. , USA
24. Ozes, O.N., Mayo, L.D., Gustin, J.A., Pfeffer, S.R., Pfeffer, L.M., Donner, D.B., NF-?B activation by tumour necrosis factor requires the Akt serine-threonine kinase (1999) Nature (Lond), 401, pp. 82-85
25. Romashkova, J.A., Makarov, S.S., NF-?B is a target of AKT in anti-apoptotic PDGF signaling (1999) Nature (Lond), 401, pp. 86-90
26. Schmitz, M.L., Baeuerle, P.A., The p65 subunit is responsible for the strong transcription activating potential of NF-?B (1991) EMBO (Eur Mol Biol Organ) J, 10, pp. 3805-3817
27. Viatour, P., Merville, M.P., Bours, V., Chariot, A., Phosphorylation of NF-?B and I?B proteins: Implications in cancer and inflammation (2005) Trends Biochem Sci, 30, pp. 43-52
28. Vo, V.C., (1997) Dictionary of Vietnamese Medicinal Plants, , Publishing House Medicine, Ho Chi Minh City, Vietnam
29. Wu, J.T., Kral, J.G., The NF-?B/I?B signaling system: A molecular target in breast cancer therapy (2005) J Surg Res, 123, pp. 158-169
30. Zandi, E., Karin, M., Bridging the gap: Composition, regulation and physiological function of the I?B kinase complex (1999) Mol Cell Biol, 19, pp. 4547-4551
31. Zandi, E., Rothwarf, D.M., Delhase, M., Hayakawa, M., Karin, M., The I?B kinase complex (IKK) contains two kinase subunits, IKK? and IKK?, necessary for I?B phosphorylation and NF-?B activation (1997) Cell, 91, pp. 243-252