[J Pharmacol Exp Ther.](https://www.ncbi.nlm.nih.gov/pubmed/16728591) 2006 Sep;318(3):1375-87. Epub 2006 May 25.

**Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma.**

[Ligresti A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ligresti%20A%5BAuthor%5D&cauthor=true&cauthor_uid=16728591)1, [Moriello AS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Moriello%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Starowicz K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Starowicz%20K%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Matias I](https://www.ncbi.nlm.nih.gov/pubmed/?term=Matias%20I%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Pisanti S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pisanti%20S%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [De Petrocellis L](https://www.ncbi.nlm.nih.gov/pubmed/?term=De%20Petrocellis%20L%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Laezza C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Laezza%20C%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Portella G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Portella%20G%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Bifulco M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bifulco%20M%5BAuthor%5D&cauthor=true&cauthor_uid=16728591), [Di Marzo V](https://www.ncbi.nlm.nih.gov/pubmed/?term=Di%20Marzo%20V%5BAuthor%5D&cauthor=true&cauthor_uid=16728591).

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/16728591)

**Abstract**

Delta(9)-Tetrahydrocannabinol (THC) exhibits antitumor effects on various cancer cell types, but its use in chemotherapy is limited by its psychotropic activity. We investigated the antitumor activities of other plant cannabinoids, i.e., cannabidiol, cannabigerol, cannabichromene, cannabidiol acid and THC acid, and assessed whether there is any advantage in using Cannabis extracts (enriched in either cannabidiol or THC) over pure cannabinoids. Results obtained in a panel of tumor cell lines clearly indicate that, of the five natural compounds tested, cannabidiol is the most potent inhibitor of cancer cell growth (IC(50) between 6.0 and 10.6 microM), with significantly lower potency in noncancer cells. The cannabidiol-rich extract was equipotent to cannabidiol, whereas cannabigerol and cannabichromene followed in the rank of potency. Both cannabidiol and the cannabidiol-rich extract inhibited the growth of xenograft tumors obtained by s.c. injection into athymic mice of human MDA-MB-231 breast carcinoma or rat v-K-ras-transformed thyroid epithelial cells and reduced lung metastases deriving from intrapaw injection of MDA-MB-231 cells. Judging from several experiments on its possible cellular and molecular mechanisms of action, we propose that cannabidiol lacks a unique mode of action in the cell lines investigated. At least for MDA-MB-231 cells, however, our experiments indicate that cannabidiol effect is due to its capability of inducing apoptosis via: direct or indirect activation of cannabinoid CB(2) and vanilloid transient receptor potential vanilloid type-1 receptors and cannabinoid/vanilloid receptor-independent elevation of intracellular Ca(2+) and reactive oxygen species. Our data support the further testing of cannabidiol and cannabidiol-rich extracts for the potential treatment of cancer.

[Mol Cancer Ther.](https://www.ncbi.nlm.nih.gov/pubmed/21566064) 2011 Jul;10(7):1161-72. doi: 10.1158/1535-7163.MCT-10-1100. Epub 2011 May 12.

**Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy.**

[Shrivastava A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shrivastava%20A%5BAuthor%5D&cauthor=true&cauthor_uid=21566064)1, [Kuzontkoski PM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kuzontkoski%20PM%5BAuthor%5D&cauthor=true&cauthor_uid=21566064), [Groopman JE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Groopman%20JE%5BAuthor%5D&cauthor=true&cauthor_uid=21566064), [Prasad A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Prasad%20A%5BAuthor%5D&cauthor=true&cauthor_uid=21566064).

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/21566064)

**Abstract**

Cannabidiol (CBD), a major nonpsychoactive constituent of cannabis, is considered an antineoplastic agent on the basis of its in vitro and in vivo activity against tumor cells. However, the exact molecular mechanism through which CBD mediates this activity is yet to be elucidated. Here, we have shown CBD-induced cell death of breast cancer cells, independent of cannabinoid and vallinoid receptor activation. Electron microscopy revealed morphologies consistent with the coexistence of autophagy and apoptosis. Western blot analysis confirmed these findings. We showed that CBD induces endoplasmic reticulum stress and, subsequently, inhibits AKT and mTOR signaling as shown by decreased levels of phosphorylated mTOR and 4EBP1, and cyclin D1. Analyzing further the cross-talk between the autophagic and apoptotic signaling pathways, we found that beclin1 plays a central role in the induction of CBD-mediated apoptosis in MDA-MB-231 breast cancer cells. Although CBD enhances the interaction between beclin1 and Vps34, it inhibits the association between beclin1 and Bcl-2. In addition, we showed that CBD reduces mitochondrial membrane potential, triggers the translocation of BID to the mitochondria, the release of cytochrome c to the cytosol, and, ultimately, the activation of the intrinsic apoptotic pathway in breast cancer cells. CBD increased the generation of reactive oxygen species (ROS), and ROS inhibition blocked the induction of apoptosis and autophagy. Our study revealed an intricate interplay between apoptosis and autophagy in CBD-treated breast cancer cells and highlighted the value of continued investigation into the potential use of CBD as an antineoplastic agent.

[Breast Cancer Res Treat.](https://www.ncbi.nlm.nih.gov/pubmed/20859676) 2011 Aug;129(1):37-47. doi: 10.1007/s10549-010-1177-4. Epub 2010 Sep 22.

**Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis.**

[McAllister SD](https://www.ncbi.nlm.nih.gov/pubmed/?term=McAllister%20SD%5BAuthor%5D&cauthor=true&cauthor_uid=20859676)1, [Murase R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Murase%20R%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Christian RT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Christian%20RT%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Lau D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lau%20D%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Zielinski AJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zielinski%20AJ%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Allison J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Allison%20J%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Almanza C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Almanza%20C%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Pakdel A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pakdel%20A%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Lee J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lee%20J%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Limbad C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Limbad%20C%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Liu Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Liu%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Debs RJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Debs%20RJ%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Moore DH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Moore%20DH%5BAuthor%5D&cauthor=true&cauthor_uid=20859676), [Desprez PY](https://www.ncbi.nlm.nih.gov/pubmed/?term=Desprez%20PY%5BAuthor%5D&cauthor=true&cauthor_uid=20859676).

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/20859676)

**Erratum in**

* Breast Cancer Res Treat. 2012 May;133(1):401-4.

**Abstract**

Invasion and metastasis of aggressive breast cancer cells are the final and fatal steps during cancer progression. Clinically, there are still limited therapeutic interventions for aggressive and metastatic breast cancers available. Therefore, effective, targeted, and non-toxic therapies are urgently required. Id-1, an inhibitor of basic helix-loop-helix transcription factors, has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. We previously reported that cannabidiol (CBD), a cannabinoid with a low toxicity profile, down-regulated Id-1 gene expression in aggressive human breast cancer cells in culture. Using cell proliferation and invasion assays, cell flow cytometry to examine cell cycle and the formation of reactive oxygen species, and Western analysis, we determined pathways leading to the down-regulation of Id-1 expression by CBD and consequently to the inhibition of the proliferative and invasive phenotype of human breast cancer cells. Then, using the mouse 4T1 mammary tumor cell line and the ranksum test, two different syngeneic models of tumor metastasis to the lungs were chosen to determine whether treatment with CBD would reduce metastasis in vivo. We show that CBD inhibits human breast cancer cell proliferation and invasion through differential modulation of the extracellular signal-regulated kinase (ERK) and reactive oxygen species (ROS) pathways, and that both pathways lead to down-regulation of Id-1 expression. Moreover, we demonstrate that CBD up-regulates the pro-differentiation factor, Id-2. Using immune competent mice, we then show that treatment with CBD significantly reduces primary tumor mass as well as the size and number of lung metastatic foci in two models of metastasis. Our data demonstrate the efficacy of CBD in pre-clinical models of breast cancer. The results have the potential to lead to the development of novel non-toxic compounds for the treatment of breast cancer metastasis, and the information gained from these experiments broaden our knowledge of both Id-1 and cannabinoid biology as it pertains to cancer progression.

**Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells.**

[McAllister SD](https://www.ncbi.nlm.nih.gov/pubmed/?term=McAllister%20SD%5BAuthor%5D&cauthor=true&cauthor_uid=18025276)1, [Christian RT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Christian%20RT%5BAuthor%5D&cauthor=true&cauthor_uid=18025276), [Horowitz MP](https://www.ncbi.nlm.nih.gov/pubmed/?term=Horowitz%20MP%5BAuthor%5D&cauthor=true&cauthor_uid=18025276), [Garcia A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Garcia%20A%5BAuthor%5D&cauthor=true&cauthor_uid=18025276), [Desprez PY](https://www.ncbi.nlm.nih.gov/pubmed/?term=Desprez%20PY%5BAuthor%5D&cauthor=true&cauthor_uid=18025276).

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/18025276)

**Abstract**

Invasion and metastasis of aggressive breast cancer cells is the final and fatal step during cancer progression, and is the least understood genetically. Clinically, there are still limited therapeutic interventions for aggressive and metastatic breast cancers available. Clearly, effective and nontoxic therapies are urgently required. Id-1, an inhibitor of basic helix-loop-helix transcription factors, has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. Using a mouse model, we previously determined that metastatic breast cancer cells became significantly less invasive in vitro and less metastatic in vivo when Id-1 was down-regulated by stable transduction with antisense Id-1. It is not possible at this point, however, to use antisense technology to reduce Id-1 expression in patients with metastatic breast cancer. Here, we report that cannabidiol (CBD), a cannabinoid with a low-toxicity profile, could down-regulate Id-1 expression in aggressive human breast cancer cells. The CBD concentrations effective at inhibiting Id-1 expression correlated with those used to inhibit the proliferative and invasive phenotype of breast cancer cells. CBD was able to inhibit Id-1 expression at the mRNA and protein level in a concentration-dependent fashion. These effects seemed to occur as the result of an inhibition of the Id-1 gene at the promoter level. Importantly, CBD did not inhibit invasiveness in cells that ectopically expressed Id-1. In conclusion, CBD represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumor aggressiveness.

[Toxicol Lett.](https://www.ncbi.nlm.nih.gov/pubmed/22963825) 2012 Nov 15;214(3):314-9. doi: 10.1016/j.toxlet.2012.08.029. Epub 2012 Sep 8.

**Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.**

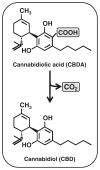
[Takeda S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Takeda%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22963825)1, [Okajima S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Okajima%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Miyoshi H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Miyoshi%20H%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Yoshida K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yoshida%20K%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Okamoto Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Okamoto%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Okada T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Okada%20T%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Amamoto T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Amamoto%20T%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Watanabe K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Watanabe%20K%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Omiecinski CJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Omiecinski%20CJ%5BAuthor%5D&cauthor=true&cauthor_uid=22963825), [Aramaki H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aramaki%20H%5BAuthor%5D&cauthor=true&cauthor_uid=22963825).

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/22963825)

**Abstract**

Cannabidiol (CBD), a major non-psychotropic constituent of fiber-type cannabis plant, has been reported to possess diverse biological activities, including anti-proliferative effect on cancer cells. Although CBD is obtained from non-enzymatic decarboxylation of its parent molecule, cannabidiolic acid (CBDA), few studies have investigated whether CBDA itself is biologically active. Results of the current investigation revealed that CBDA inhibits migration of the highly invasive MDA-MB-231 human breast cancer cells, apparently through a mechanism involving inhibition of cAMP-dependent protein kinase A, coupled with an activation of the small GTPase, RhoA. It is established that activation of the RhoA signaling pathway leads to inhibition of the mobility of various cancer cells, including MDA-MB-231 cells. The data presented in this report suggest for the first time that as an active component in the cannabis plant, CBDA offers potential therapeutic modality in the abrogation of cancer cell migration, including aggressive breast cancers.

### Items: 6

1. [](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

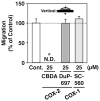
[Fig. 1. From: Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

Chemical structures of CBDA and CBD. In the fiber-type cannabis plant, the concentration of CBD is much lower than that of its precursor CBDA. CBD is formed artificially from CBDA by non-enzymatic decarboxylation during extraction step ().

Shuso Takeda, et al. Toxicol Lett. ;214(3):314-319.

[Citation](https://www.ncbi.nlm.nih.gov/pubmed/22963825)[Full text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

2.

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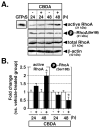
[Fig. 4. From: Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

COX-2 inhibitory activity of CBDA is not essential to attenuate MDA-MB-231 cell migration. Transwell migration assays were performed to determine the effects of COX-2 selective inhibitors (25 μM CBDA or 25 DuP-697) and COX-1selective inhibitor (25 μM SC-560) on MDA-MB-231 cell migration 12 h after their respective treatments. Data are expressed as the percent of vehicle-treated group (indicated as Cont.), as mean ± S.D. (*n* = 8). \*Significantly different (*p* < 0.05) from the vehicle-treated control. N.D., not detectable due to complete inhibition of the migration.

Shuso Takeda, et al. Toxicol Lett. ;214(3):314-319.

[Citation](https://www.ncbi.nlm.nih.gov/pubmed/22963825)[Full text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

3.

[](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

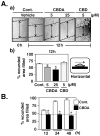
[Fig. 5. From: Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

CBDA stimulates RhoA activity. (A) RhoA affinity pull-down assays were used to determine the level of active RhoA according to the methods described in Section 2. Resulted pull-down samples were subjected to Western blot analyses using an anti-RhoA antibody. Active RhoA was increased by 25 μM CBDA (indicated as +) in a time-dependent manner. Western blot analyses were also performed using an anti-RhoA antibody specific to RhoA phosphorylated at Ser188 and a β-actin antibody. (B) Results are expressed as the ratio of active RhoA to total RhoA protein in each cell lysate. Data are expressed as the fold change *vs.* vehicle-treated group (indicated as −), as mean ± S.D. (*n* = 3). \*Significantly different (*p*< 0.05) from the vehicle-treated control.

Shuso Takeda, et al. Toxicol Lett. ;214(3):314-319.

[Citation](https://www.ncbi.nlm.nih.gov/pubmed/22963825)[Full text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

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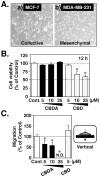
[Fig. 3. From: Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

Effect of CBDA on the horizontal migration of MDA-MB-231 cells. (A) Wound-healing assays (horizontal migration) were performed to determine the effects of CBDA or CBD on MDA-MB-231 cell migration. (a) Representative images of the migrating cells were captured 12 h after vehicle (indicated as Cont.), 5 μM or 25 μM CBDA and 5 μM CBD treatments. (b) Migration data presented in panel (a) was assessed on the basis of percent wounded area filled in. Data are expressed as the percent of vehicle-treated group (indicated as Cont.), as mean ± S.D. (*n* = 8). (B) Migration data was assessed on the basis of percent wounded area filled in 12, 24, or 48 h after treatments with 25 μM CBDA. Data are expressed as the percent of vehicle-treated group (indicated as Cont.), as mean ± S.D. (*n* = 8) \*Significantly different (*p* < 0.05) from the respective vehicle-treated controls.

Shuso Takeda, et al. Toxicol Lett. ;214(3):314-319.

[Citation](https://www.ncbi.nlm.nih.gov/pubmed/22963825)[Full text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

5.

[](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

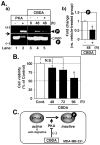
[Fig. 2. From: Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

Effect of CBDA on the vertical migration of highly aggressive human breast cancer MDA-MB-231 cells. (A) Morphologies of two human breast cancer cell lines; MCF-7 cells (a) and MDA-MB-231 cells (b). MCF-7 cells display epithelial morphology (*collective*) and MDA-MB-231 cells display single elongated morphology (*mesenchymal*). (B) MDA-MB-231 cells were exposed for 12 h to CBDA (5, 10, 25 μM) and CBD (5, 10, 25 μM). After the treatments, cell viability was measured according to the methods described in Section 2. Data are expressed as the percent of vehicle-treated group (indicated as Cont.), as mean ± S.D. (*n* = 6). \*Significantly different (*p* < 0.05) from the vehicle-treated control. (C) Transwell migration assays (vertical migration) were performed to determine MDA-MB-231 cell migration 12 h after treatments with 5 μM, 10 μM, or 25 μM CBDA and 5 μM CBD. Data are expressed as the percent of vehicle-treated group (indicated as Cont.), as mean ± S.D. (*n* = 8). \*Significantly different (*p* < 0.05) from the vehicle-treated control. N.D., not detectable due to complete inhibition of the migration.

Shuso Takeda, et al. Toxicol Lett. ;214(3):314-319.

[Citation](https://www.ncbi.nlm.nih.gov/pubmed/22963825)[Full text](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

6.

[](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

[Fig. 6. From: Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009504/)

CBDA inhibits PKA activity. (A) (a) A representative photograph of phosphorylated bands and non-phosphorylated bands of PKA-specific substrate peptide in MDA-MB-231 cells incubated with vehicle (time 0, lane 3), vehicle (48 h, lane 4), and 25 μM CBDA (48 h, lane 5) was shown. For positive and negative controls, the reactions were performed in the presence (lane 1) or absence (lanes 2) of PKA catalytic subunit, respectively. An arrow in the image indicates wells that samples are applied. (b) The relative intensity of phosphorylated bands in MDA-MB-231 cells is shown. Data are expressed as fold change *vs.* non-CBDA-treated group (left panel; lanes 4 *vs.* 5), as mean ± S.D. (*n* = 3). \*Significantly different (*p* < 0.05) from the vehicle-treated control. (B) MDA-MB-231 cells were treated with vehicle (indicated as Cont.) or 25 μM CBDA for 48, 72, or 96 h. After the treatments, cell viability was measured according to the methods described in Section 2. Data are expressed as the percent of vehicle-treated group, as mean ± S.D. (*n* = 6). \*Significantly different (*p* < 0.05) from the vehicle-treated control. N.S., not significant. (C) A model of CBDA-mediated RhoA activation through PKA inhibition.

Shuso Takeda, et al. Toxicol Lett. ;214(3):314-319.

[J Nat Med.](https://www.ncbi.nlm.nih.gov/pubmed/27530354) 2017 Jan;71(1):286-291. doi: 10.1007/s11418-016-1030-0. Epub 2016 Aug 16.

**Cannabidiolic acid-mediated selective down-regulation of c-fos in highly aggressive breast cancer MDA-MB-231 cells: possible involvement of its down-regulation in the abrogation of aggressiveness.**

[Takeda S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Takeda%20S%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)1,2, [Himeno T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Himeno%20T%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)2, [Kakizoe K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kakizoe%20K%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)2, [Okazaki H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Okazaki%20H%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)2, [Okada T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Okada%20T%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)3, [Watanabe K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Watanabe%20K%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)4, [Aramaki H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aramaki%20H%5BAuthor%5D&cauthor=true&cauthor_uid=27530354)5,6.

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/27530354)

**Abstract**

The physiological activities of cannabidiolic acid (CBDA), a component of fiber-type cannabis plants, have been demonstrated and include its function as a protector against external invasion by inducing cannabinoid-mediated necrosis (Shoyama et al., Plant Signal Behav 3:1111-1112, 2008). The biological activities of CBDA have been attracting increasing attention. We previously identified CBDA as an inhibitor of the migration of MDA-MB-231 cells, a widely used human breast cancer cell line in cancer biology, due to its highly aggressive nature. The chemical inhibition and down-regulation of cyclooxygenase-2 (COX-2), the expression of which has been detected in ~40 % of human invasive breast cancers, are suggested to be involved in the CBDA-mediated abrogation of cell migration. However, the molecular mechanism(s) responsible for the CBDA-induced down-regulation of COX-2 in MDA-MB-231 cells have not yet been elucidated. In the present study, we describe a possible mechanism by which CBDA abrogates the expression of COX-2 via the selective down-regulation of c-fos, one component of the activator protein-1 (AP-1) dimer complex, a transcription factor for the positive regulation of the COX-2 gene.

**KEYWORDS:**

Cannabidiolic acid; Cyclooxygenase-2; Fiber-type cannabis plant; MDA-MB-231 cells; c-fos