Natural derivatives of curcumin attenuate the Wnt/beta-catenin pathway through down-regulation of the transcriptional coactivator p300. Biochem Biophys Res Commun

ARTICLE *in* BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS · DECEMBER 2008

Impact Factor: 2.3 · DOI: 10.1016/j.bbrc.2008.10.171 · Source: PubMed

Biochemical and Biophysical Research Communications 377 (2008) 1304–1308

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Natural derivatives of curcumin attenuate the Wnt/β-catenin pathway through down-regulation of the transcriptional coactivator p300

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ARTICLE INFO

Article history:
Received 30 October 2008
Available online 10 November 2008

Keywords:
Bisdemethoxycurcumin
Demethoxycurcumin
p300
Wnt/β-catenin pathway

ABSTRACT

Curcumin, a component of turmeric (*Curcuma longa*), has been reported to suppress β-catenin response transcription (CRT), which is aberrantly activated in colorectal cancer. However, the effects of its natural analogs (demethoxycurcumin [DMC] and bisdemethoxycurcumin [BDMC]) and metabolite (tetrahydrocurcumin [THC]) on the Wnt/β-catenin pathway have not been investigated. Here, we show that DMC and BDMC suppressed CRT that was activated by Wnt3a conditioned-medium (Wnt3a-CM) without altering the level of intracellular β-catenin, and inhibited the growth of various colon cancer cells, with comparable potency to curcumin. Additionally, DMC and BDMC down-regulated p300, which is a positive regulator of the Wnt/β-catenin pathway. Notably, THC also inhibited CRT and cell proliferation, but to a much lesser degree than curcumin, DMC, or BDMC, indicating that the conjugated bonds in the central seven-carbon chain of curcuminoids are essential for the inhibition of Wnt/β-catenin pathway and the anti-proliferative activity of curcuminoids. Thus, our findings suggest that curcumin derivatives inhibit the Wnt/β-catenin pathway by decreasing the amount of the transcriptional coactivator p300.

The Wnt/β-catenin pathway, which is activated by the interaction of Wnt1, Wnt3a, and Wnt8 with Fz receptors and low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors, plays important roles in cell proliferation, differentiation, and oncogenesis [1]. Central to this pathway is the level of cytosolic β-catenin, which regulates its target genes. In the absence of a Wnt signal, β-catenin is phosphorylated by both casein kinase 1 (CK1) and glycogen synthase kinase-3β (GSK-3β), and then forms a complex with adenomatous polyposis coli (APC)/Axin. This destruction complex is then recognized by F-box β-transducin repeat-containing protein (β-TrCP), a component of the ubiquitin ligase complex, resulting in the degradation of β-catenin [2–4]. Activation of the receptor by its Wnt ligands negatively regulates the destruction complex and leads to cytoplasmic α-catenin stabilization [5].

Dysregulation of the Wnt/β-catenin pathway is a frequent early event in intestinal epithelial cells during the development of colon cancer [6]. Mutations of the APC gene occur in the majority of sporadic colorectal cancers, as well as in familial adenomatous polyposis (FAP) [7]. Additionally, mutations in the β-catenin gene have been observed in colorectal cancer and melanoma [8]. These mutations lead to the excessive accumulation of β-catenin in the nucleus, where it interacts with the T-cell factor/lymphocyte enhancer factor (TCF/LEF) family and p300 [9] and promotes the transcription of its target genes, which play important roles in colorectal tumorigenesis [10,11].

Curcumin, the yellow pigment isolated from turmeric, has been shown to inhibit the proliferation of colon, breast, prostate, esophagus, and lung cancer cells [12,13], and is currently being assessed clinically for the treatment of various cancers [14]. Curcumin mediates anti-proliferative effects through several pathways, such as the suppression of β-catenin/TCF transactivation [15,16] and *cyclin D1* expression [16]. It also induces apoptosis via the activation of caspase and p53 [17,18], and exerts anti-angiogenic effects via the down-regulation of vascular endothelial growth factor (VEGF) [19]. Because commercially available curcumin used for research and clinical trials (curcumin mix) also contains 17% DMC and 3% BDMC, in addition to curcumin itself, we evaluated the inhibitory activity of DMC and BDMC on the Wnt/β-catenin pathway and the proliferation of colon cancer cells. We also examined the molecular mechanism(s) by which DMC and BDMC suppress the Wnt/β-catenin pathway. Additionally, the effects of THC, one of the major metabolites of curcumin in the cell, were examined.

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doi:10.1016/j.bbrc.2008.10.171

Materials and methods

Chemicals and plasmids. Curcumin, DMC, BDMC, and THC were prepared from the dried rhizomes of *C. longa* as described previously [20] and were then dissolved in DMSO. Human Frizzled-1 (hFz-1) cDNA was cloned as described previously [21]. The pTOPFlash and pFOPFlash reporter plasmids were obtained from Upstate Biotechnology (Lake Placid, NY, USA). Secreted alkaline phosphatase (SEAP) reporter plasmid was constructed by insertion of five copies TCF/LEF-binding site (AAGATCAAAGGGGGT) to E1b minimal promoter. p300 expression plasmid was a gift from Y. Nakatani (Harvard Medical School, Boston, MA).

Cell culture, transfection, and reporter assay. L cells that secrete Wnt3a, HEK293 cells, SW480, HCT116, DLD-1, and HCT-15 cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained in DMEM supplemented with 10% fetal bovine serum (FBS), 120 μg penicillin/ml, and 200 μg streptomycin/ml. Wnt3a-conditioned medium (Wnt3a-CM) was prepared as previously described [21]. Transfection was performed with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Luciferase assay was performed using the Dual Luciferase Assay Kit (Promega, Madison, WI, USA) and secreted alkaline phosphatase assay was carried out using Phospha-Light™ Assay kit (Applied Biosystems, CA, USA).

Establishment of HEK293 reporter cell lines. HEK 293 reporter (TOPFlash) and control (FOPFlash) cells were established as previously described [22]. The HEK293 reporter (SEAP) cell line was established by selecting HEK293 cells co-transfected with the plasmid expressing hFz-1 and SEAP reporter plasmid, using media containing G418 (1 mg/ml). The cells were inoculated into 96-well plates at 15,000 cells per well in duplicate and grown for 24 h. Wnt3a-CM was added, and then curcuminoids were added to the wells. After 15 h, the plates were assayed for FL activity or SEAP activity and cell viability.

Western blotting. The cytosolic and nuclear fractions were prepared as previously described [23]. Proteins were separated by SDS–PAGE in a 4–12% gradient gel (Invitrogen) and transferred to nitrocellulose membranes (Bio-Rad, Hercules, CA, USA). The membranes were blocked with 5% nonfat milk and probed with anti-β-catenin (BD Transduction Laboratories, Lexington, KY, USA), anti-TCF-4 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), anti-p300 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), and anti-actin antibodies (Cell Signaling Technology, Beverly, MA, USA). The membranes were then incubated with horseradish-peroxidase-conjugated anti-mouse IgG or anti-rabbit IgG (Santa Cruz Biotechnology) and visualized using the ECL system (Santa Cruz Biotechnology).

Cell viability assay. Cells were inoculated into 96-well plates and treated with curcumin, DMC, BDMC, and THC for 48 h. The cell viability from each treated sample was measured in triplicate using Celltiter-Glo assay kit (Promega) according to the manufacturer's instructions.

Results and discussion

Curcumin derivatives inhibit the Wnt/β-catenin pathway

Curcumin has two methoxy groups at its *ortho* position, whereas DMC contains only one and BDMC has none (Fig. 1). In comparison, THC possesses two methoxy groups, but lacks the conjugated bond in the central seven-carbon chain (Fig. 1). We evaluated the ability of curcumin, its natural analogs, DMC and BDMC, and THC to inhibit the Wnt/β-catenin pathway using HEK293 reporter cells stably transfected with a synthetic β-catenin/Tcf-dependent firefly luciferase (FL) reporter and hFz-1 expression plasmids. When HEK293 reporter cells were treated with Wnt3a-CM, FL activity increased dramatically (Fig. 2A). Incubation with curcumin resulted in a dose-dependent decrease in FL activity, which was activated by Wnt3a-conditioned medium (Fig. 2A). In addition, DMC and BDMC inhibited Wnt3a-induced FL activity, with potencies similar to curcumin, approximately 90% of CRT was blocked at a concentration of 40 μM DMC and BDMC. In contrast, THC was much less effective at inhibiting Wnt3a-induced FL activity (Fig. 2A). Curcumin, DMC, BDMC, and THC did not affect mutated β-catenin/Tcf-dependent luciferase reporter activity under these conditions (Fig. 2A). We also confirmed the inhibitory effects of curcumin and its analogs on the Wnt/β-catenin pathway using other HEK293 reporter cells stably transfected with a synthetic β-catenin/Tcf-dependent secreted alkaline phosphatase (SEAP) reporter and hFz-1 expression plasmids. Consistent with results from the luciferase reporter assay, curcumin, DMC, and BDMC inhibited Wnt3a-induced SEAP activity in a concentration-dependent manner, whereas THC was less active (Fig. 2B). Taken together, these results indicate that curcumin and its natural analogs (DMC and BDMC) specifically inhibit the Wnt/β-catenin pathway.

Curcumin derivatives do not affect the level of β-catenin

The Wnt/β-catenin pathway is primarily dependent on the level of intracellular β-catenin, which is controlled by ubiquitin-dependent proteolysis [24]. Moreover, previous reports indicate that curcumin regulates intracellular β-catenin levels via mechanisms such as promoting caspase-3-mediated cleavage of β-catenin or reducing the amount of nuclear β-catenin [15,16]. Thus, we examined whether curcumin and its derivatives affected intracellular β-catenin levels via Western blot analysis with an anti-β-catenin antibody. Curcumin did not affect β-catenin levels in the cytoplasm or nucleus at a concentration of 20 μM, at which CRT was suppressed approximately 30% (Fig. 3A). However, we observed the degradation of cytoplasmic β-catenin and decreased nuclear β-catenin levels upon treatment with a higher concentration of curcumin (40 μM, Fig. 3A), consistent with previous reports [15,16]. Interestingly, in contrast to CRT, DMC and BDMC did not affect cytoplasmic or nuclear β-catenin levels at any of the tested concentrations (Fig. 3A). These results indicate that a novel mechanism, other than the above-described mechanisms, may mediate inhibition of the Wnt/β-catenin pathway by these natural analogs of curcumin.

Curcumin derivatives down-regulate the p300 coactivator

It has been reported that β-catenin forms a complex with TCF-4 and the p300 coactivator, to generate a transcriptionally active complex [9]. Thus, to uncover the mechanism(s) by which curcumin derivatives suppress the Wnt/β-catenin pathway, we next examined the effects of DMC and BDMC on nuclear levels of TCF-4 and p300 via Western blot analysis. Nuclear TCF-4 level did not change in response to DMC or BDMC (Fig. 3B); however, incubation with DMC and BDMC dramatically reduced the level of p300 coactivator in the nucleus, in a dose-dependent manner (Fig. 3C). We also observed that the ectopic expression of p300 partially abolished DMC- and BDMC-mediated CRT inhibition (Fig. 3D). These results suggest that curcumin derivatives attenuate the Wnt/β-catenin pathway via down-regulation of p300. As expected, THC did not affect the level of intracellular β-catenin, TCF-4, or p300, consistent with results from CRT (Fig. 3A, B, and C).

Curcumin derivatives inhibit proliferation of various colon cancer cells

Several studies have reported that the disruption of β-catenin/Tcf function suppressed the proliferation of human colon cancer cells [25]. Moreover, β-catenin/Tcf-dependent gene products are

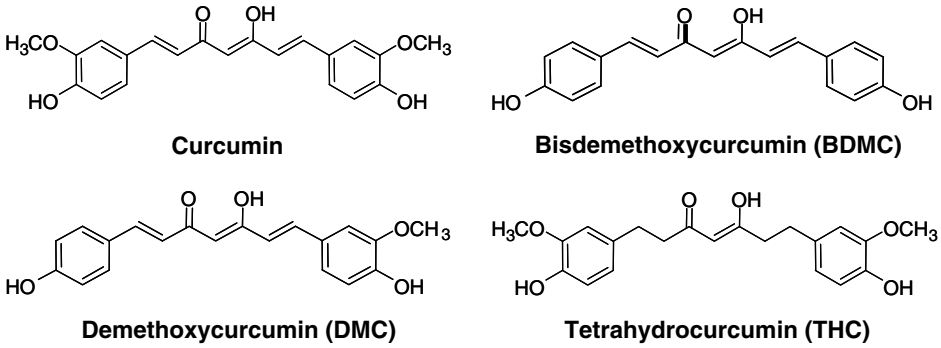

Fig. 1. Chemical structures of curcumin and related β-diketone derivatives isolated from *Curcuma longa*.

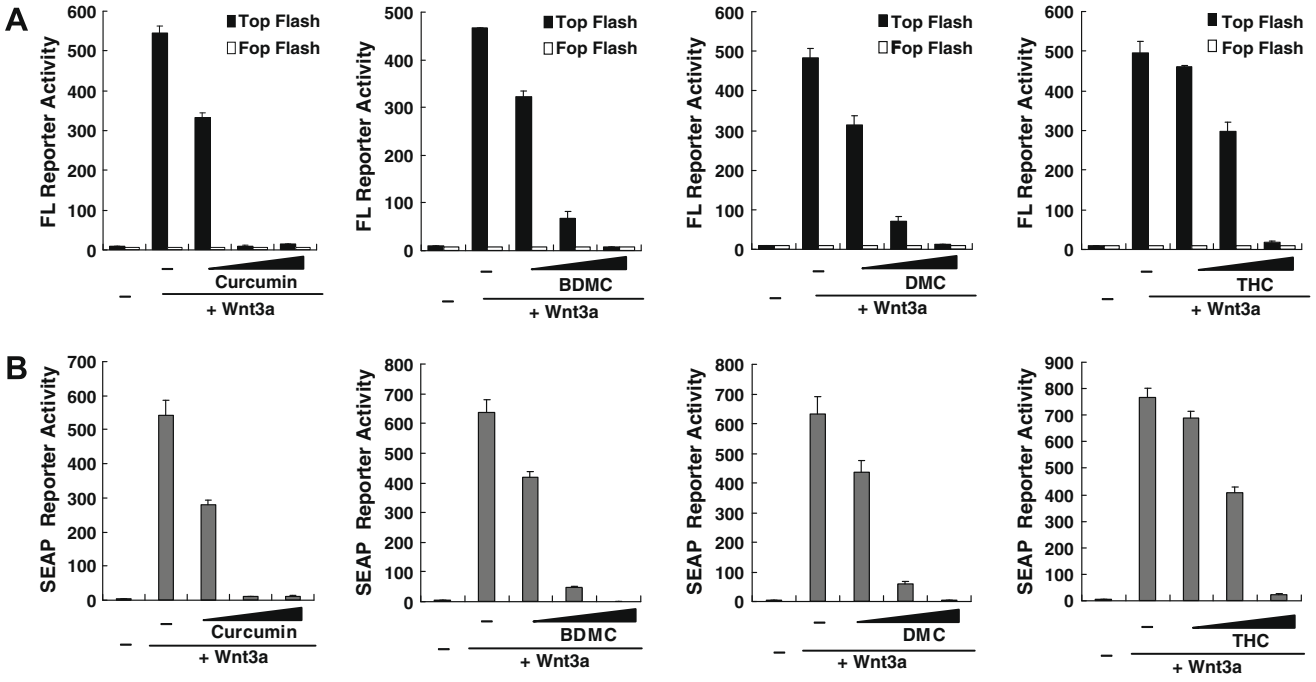

Fig. 2. Inhibition of Wnt/β-catenin pathway by curcuminoids. HEK293 reporter and control cells were incubated with either vehicle (DMSO) or curcuminoids (20 and 40 μm) in the presence of Wnt3a-CM. After 15 h, luciferase activity (A) or SEAP activity (B) was determined. The results are the average of three experiments, and the bars indicate standard deviations.

known to regulate cell proliferation and apoptosis [10,11]. For example, cyclin D1, which forms a complex with cyclin-dependent kinase 4/6, mediates growth factor-dependent G1 phase progression [26]. We examined the effect of curcumin, DMC, BDMC, and THC on the growth of various colon cancer cells. Curcumin, DMC, and BDMC suppressed the proliferation of various colon cancer cell lines, including SW480, HCT116, DLD-1, and HCT15, with comparable potency, whereas THC was less effective (Fig. 4). These results suggest that the anti-proliferative activities of the various curcuminoids correlate with their inhibitory effects on the Wnt/β-catenin pathway.

Curcumin has been demonstrated to prevent the proliferation of colon cancer cells through the suppression of β-catenin/TCF transactivation [15,16]. In this study, we showed that DMC and BDMC, natural analogs in the commercially available curcumin mixture used for research and clinical trials, exhibited inhibitory effects on the Wnt/β-catenin pathway through down-regulation of the transcriptional coactivator p300. Previous studies have demonstrated that p300 is a positive regulator in the Wnt/β-catenin pathway. Ectopic expression of p300 activates CRT and inhibition of this gene reduces TOPflash activity [9,27]. This histone acetyltransferase (HAT) can interact with β-catenin *in vitro* [9,27] and is recruited to β-catenin response elements in the cyclin D2, c-Myc, and survivin genes upon activation of the Wnt/β-catenin pathway [28–30]. Additionally, p300 mediates the acetylation of β-catenin and then increases interaction with TCF-4, thereby activating β-catenin transcriptional activity [31].

In this study, DMC and BDMC potently reduced the amount of p300 coactivator in the nucleus, suppressed the Wnt/β-catenin pathway, and inhibited the growth of various colon cancer cells. In contrast, THC, a reductive metabolite of curcumin, had a lesser effect on the down-regulation of nuclear p300, inhibition of the Wnt/β-catenin pathway, and anti-proliferative activity against colon cancer cells. These results are consistent with a previous study of the anti-proliferative activity of curcuminoids against several cancer cells [32] and indicate that the double bond in the central carbon chain of curcuminoids is necessary for the suppression of the Wnt/β-catenin pathway and its anti-proliferative activity.

In summary, we describe a new mechanism by which curcumin derivatives may regulate the Wnt/β-catenin pathway. DMC and BDMC suppressed the Wnt/β-catenin pathway by down-regulating the p300 coactivator. We also found that the conjugated bonds in

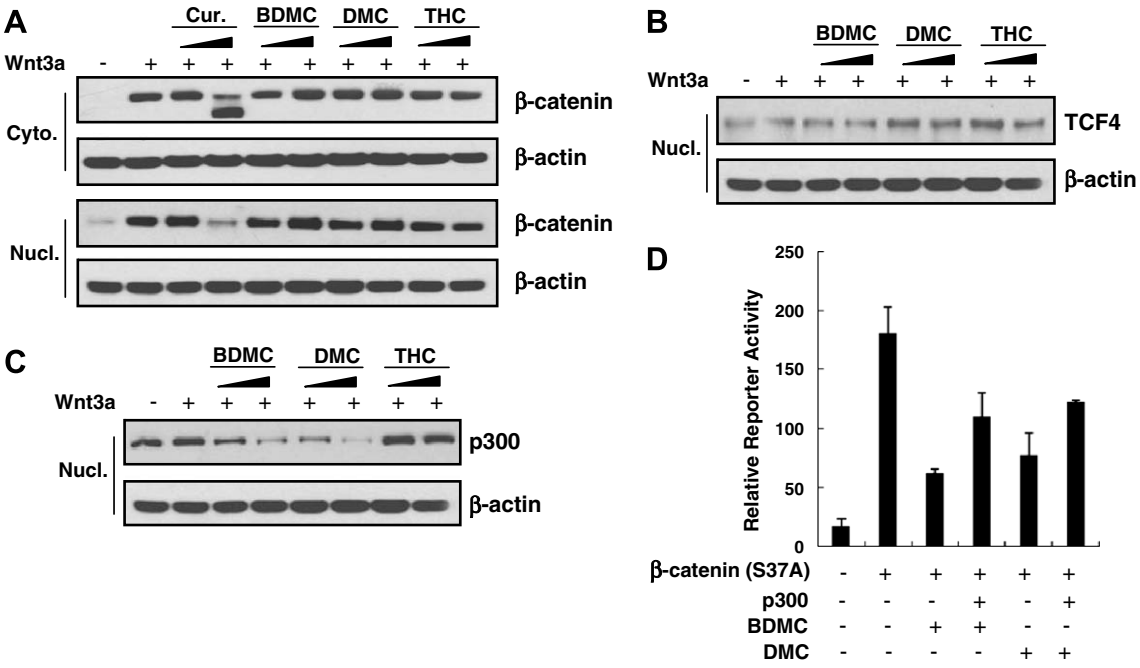

Fig. 3. Curcumin derivatives down-regulates p300 coactivator. (A–C) Cytosolic and/or nuclear proteins were prepared from HEK293 reporter cells treated with either vehicle (DMSO) or curcuminoids (20 and 40 μm) in the presence of Wnt3a-CM for 15 h and then subjected to Western blotting with anti-β-catenin (A), anti-TCF-4 (B), and Anti-p300 (C) antibodies. The blots were re-probed with anti-actin antibody as a loading control. (D) HEK293 reporter cells were co-transfected with S37A β-catenin, p300, and pCMV-RL plasmids and incubated with DMC (15 μM) or BDMC (15 μM) for 15 h. Luciferase activities were measured 39 h after transfection and normalized with RL activity. Results are the average of three experiments, and the bars indicate standard deviations.

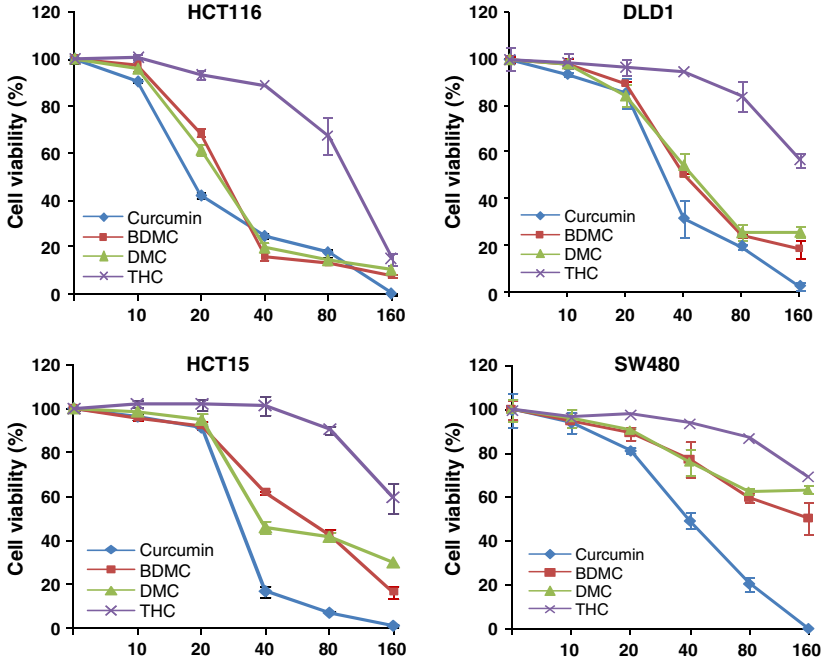

Fig. 4. Effect of curcuminoids and THC on colon cancer cell proliferation. SW480, HCT116, DLD-1, and HCT15 colon cancer cells were incubated with increasing amounts of curcuminoids and cell viability was determined by Celltiter-Glo assay (Promega). The results shown are the average of three experiments, and the bars indicate standard deviations.

the central seven-carbon chain of curcuminoid are important for its function, including inhibition of the Wnt/β-catenin pathway and cellular proliferation. Together, our findings may facilitate the development of curcumin-derived anti-neoplastic therapeutics for colon cancer.

Acknowledgments

This work was supported by the Korea Institute of Science & Technology Evaluation and Planning (KISTEP) and Ministry of Science & Technology (MOST), Korean government, through its

National Nuclear Technology Program (S. Oh) and by a 2006 Inje University Research Grant (I.-W. Choi).

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