ABSTRACT

Baicalein (5,6,7-trihydroxyflavone), a flavonoid originated from the root of Chinese medicinal herb Scutellaria baicalensis, has been shown to exert anti-inflammatory and antioxidant effects, and it is a well known inhibitor of 12-lipoxygenase. We have previously reported that neuroglia undergo nitric oxide (NO)-dependent and NO-independent apoptosis upon inflammatory activation. In the current work, we asked how anti-inflammatory baicalein influences autoregulatory apoptosis of activated microglia and their NO production. Baicalein attenuated NO production and apoptosis of lipopolysaccharide (LPS)-activated, but not interferon-γ-activated, BV-2 mouse microglial cells as well as rat primary microglia cultures. The inhibition of NO production by baicalein was due to the suppression of inducible NO synthase induction. Moreover, baicalein inhibited LPS-induced nuclear factor-κB (NF-κB) activity in BV-2 cells without affecting caspase-11 activation, interferon regulatory factor-1 induction, or signal transducer and activator of transcription-1 phosphorylation. Transfection of BV-2 cells with a p65 subunit of NF-κB abolished the apoptosis-attenuating effects of baicalein, indicating that the inhibition of NF-κB is a major mechanism of action. Baicalein, however, did not significantly affect NO donor-mediated cytotoxicity, and the apoptosis-attenuating effects of baicalein were independent of 12-lipoxygenase inhibition. Based on our previous findings that activation-induced cell death (AICD) of microglia occurs through two separate pathways (NO-dependent pathway and caspase-11-dependent pathway), our current results suggest that baicalein selectively inhibits the NO-dependent apoptotic pathway of activated microglia by suppressing cytotoxic NO production. Also, the AICD-inhibiting effects of baicalein were specific for the inflammatory stimulus that activated microglia.
of baicalein against cerebral ischemia was demonstrated in gerbils (Hamada et al., 1993). In contrast to these cytotoxic effects, numerous reports also demonstrated apoptotic-inducing and antiproliferative effects of baicalein. As a 12-lipooxygenase inhibitor, baicalein induced apoptosis of a variety of human cancer cells such as breast cancer cells (Tong et al., 2002), hepatoblastoma cells (Chang et al., 2002), prostate cancer cells (Pidgeon et al., 2002), and gastric cancer cells (Wong et al., 2001). In many cases, the apoptotic action of baicalein was associated with caspase activation, mitochondrial dysfunction, and modulation of Bel-2 family proteins. Compared with well known effects of baicalein on human cancer cells and its anti-inflammatory actions in peripheral inflammatory cells, little information is available about its effects on the inflammatory activation of microglia, their NO production, and apoptosis in central nervous system (CNS).

Microglia are a type of neuroglia that support, nurture, and protect the neurons maintaining homeostasis of the fluid that bathes neurons. Microglia function as macrophages in CNS; they migrate to the area of injured nervous tissue, and they engulf and destroy microbes and cellular debris (Gehrmann et al., 1995). Stimulated microglia produce diverse inflammatory mediators such as NO and tumor necrosis factor α. There is growing evidence that toxic mediators produced by activated microglial cells might be involved in the pathogenesis of various neurodegenerative diseases (McGeer and McGeer, 1995; Minghetti and Levi, 1998; Gonzalez-Scarano and Baltuch, 1999). Thus, in CNS, the production of toxic inflammatory mediators by activated microglial cells must be strictly regulated to avoid harmful effects. Potential mechanisms for down-regulation of activated microglia may include the deactivation or elimination of activated cells. We and others have previously shown that activated microglial cells (Lee et al., 2001b; Liu et al., 2001) and astrocytes (Suk et al., 2002) undergo apoptosis for the regulation of their own activation states, which is similar to activation-induced cell death (AICD) of lymphocytes. Because the process of autoregulatory apoptosis of neuroglial cells heavily depends on autocrine NO production (Lee et al., 2001b; Suk et al., 2002), this type of programmed cell death may be either positively or negatively influenced by exogenous factors that stimulate or inhibit NO production. Wogonin, another flavonoid found in S. baicalensis Georgi, interfered with astrocyte AICD by inhibiting NO production (Kim et al., 2001a). Based on the known anti-inflammatory activities of baicalein, we hypothesized that baicalein may modulate NO production in microglial cells, which in turn may regulate apoptosis of microglial cells. To test this hypothesis, we used BV-2 mouse microglial cells and rat primary microglia cultures, which were activated with LPS and IFNγ in the presence or absence of baicalein, and evaluated the effects of the flavonoid on NO production as well as microglial apoptosis. We also investigated the mechanism(s) by which baicalein modulates autoregulatory apoptosis of activated microglia with a focus on the apoptotic signaling pathways.

**Materials and Methods**

**Reagents.** LPS, N-monomethyl-L-arginine (NMMA), S-nitroso-N-acetylpenicillamine (SNAP), and N-acetyl cysteine (NAC) were obtained from Sigma-Aldrich (St. Louis, MO). Recombinant mouse and rat IFN-γ was purchased from R&D Systems (Minneapolis, MN). A caspase inhibitor z-Val-Ala-Asp(OMe)-CH₂F (z-VAD-fmk) and a fluorogenic caspase substrate Ac-Leu-Glu-Asp-aminomethylcoumarin (Ac-LEHD-AMC) were obtained from Calbiochem (La Jolla, CA). 5,6,7-Trihydroxyflavone (baicalein), 12(S)-hydroxyecosatetraenoic acid (HETE), and 5,8,11-eicosatriynoic acid were obtained from Cayman Chemicals (Ann Arbor, MI). All other chemicals were obtained from Sigma-Aldrich, unless stated otherwise.

**Microglial Cells.** BV-2 mouse microglial cell line originally developed by Dr. V. Bocchini at University of Perugia (Perugia, Italy) (Blasi et al., 1999) was generously provided by Dr. E. Choi at Korea University (Seoul, Korea). The cell line was maintained in Dulbecco's modified Eagle's medium supplemented with 5% fetal bovine serum, 2 mM glutamine, and penicillin-streptomycin (Invitrogen, Carlsbad, CA). Rat primary microglial cells were prepared as previously described with minor modifications (Aloisi et al., 1999; Lee et al., 2001a). In brief, forebrains of newborn Sprague-Dawley rats were chopped and dissociated by trypsinization and mechanical disruption. The cells were seeded into poly-l-lysine-coated flasks. After 24 h in vitro culture for 10 days, microglial cells were detached by rapid and gentle shaking of the culture flasks and seeded into plastic surfaces. After an additional 1-h incubation, nonadherent cells were removed by replacing culture medium. The purity of microglial cultures was greater than 92% as determined by OX-42 (Serotolli, Oxford, UK) immunocytochemical staining (data not shown).

**Assessment of Cytotoxicity by MTT Assay or Trypan Blue Exclusion Assay.** Cells (3 × 10⁴ cells in 200 μl/well for BV-2 cells, 2 × 10⁵ cells in 200 μl/well for rat primary microglial cells) were seeded in 96-well plates and treated with LPS and IFNγ for the indicated time periods. The optimal concentrations for the cytotoxic action were 100 ng/ml for LPS and 100 units/ml for IFNγ (Lee et al., 2001a,b). In some experiments, cells were pretreated with a caspase inhibitor or NAC for 1 h before LPS/IFNγ treatment. After the treatment, the medium was removed and MTT (0.5 mg/ml) was added, followed by incubation at 37°C for 4 h. After that, 20 μl/well was removed and dimethyl sulfoxide was added to the cells. After insoluble crystals were completely dissolved, absorbance at 540 nm was measured using Thermomax microplate reader (Molecular Devices Corp., Sunnyvale, CA). For trypan blue exclusion assay, cell suspension was mixed with the same volume of 0.4% trypan blue solution (Invitrogen). Afterward, the number of stained cells and the total number of cells were counted using a hemocytometer (Marienfeld, Germany).

**Nitrite Quantification.** After cells (3 × 10⁴ cells in 200 μl/well for BV-2 cells, 2 × 10⁵ cells in 200 μl/well for rat primary microglial cells) were treated with activating agents in 96-well plates, NO₂⁻ in culture supernatants was measured to assess NO production in microglial cells. Fifty microliters of sample aliquots were mixed with 50 μl of Griess reagent (1% sulfanilamide/0.1% naphthylethylene diamine dihydrochloride/2% phosphoric acid) in a 96-well plate and incubated at 25°C for 10 min. The absorbance at 550 nm was measured on a microplate reader. NaNO₂ was used as the standard to calculate NO₂⁻ concentrations.

**DNA Ploidy Analysis.** Cells were suspended in phosphate-buffered saline/5 mM EDTA and fixed by adding 100% ethanol dropwise. RNAse A (40 μg/ml) was added to reconstituted cells, and incubation was carried out at room temperature for 30 min. Propidium iodide (50 μg/ml) was then added for flow cytometric analyses (FACS Vantage; BD Biosciences, Franklin Lakes, NJ).

**Western Blot Analysis.** Cells were lysed in triple-detergent lysis buffer (50 mM Tris-HCl, pH 8.0, 150 mM NaCl, 0.02% sodium azide, 0.1% SDS, 1% NP40, 0.5% sodium deoxycholate, 1 mM phenylmethylsulfonyl fluoride). Protein concentration in cell lysates was determined using Bio-Rad protein assay kit (Hercules, CA). An equal amount of protein for each sample was separated by 8 to 12% SDS-polyacrylamide gel electrophoresis and transferred to Hybond ECL.
Baicalein Selectively Inhibits NO Production and AICD of Microglia following LPS Stimulation. We have previously demonstrated that microglia undergo AICD upon inflammatory stimulation; inflammatory activation of microglia triggers autoregulatory apoptosis by two separate signaling pathways, one being NO-dependent and the other being caspase-11-dependent but NO-independent (Lee et al., 2001a). To determine how a plant flavonoid baicalein affects this autoregulatory apoptosis of activated microglia, we first evaluated the effects of baicalein on microglial NO production and cell viability following inflammatory activation. Treatment of BV-2 mouse microglial cells with inflammatory stimuli such as LPS- and IFN-γ-induced NO production as well as a decrease in the cell viability (Figs. 1 and 2). LPS dose-dependently induced NO production, which was inversely correlated with viability of microglia (Fig. 1, A and B). Treatment of BV-2 cells with baicalein before inflammatory activation resulted in a marked decrease in NO production (Fig. 1C). Baicalein pretreatment also attenuated AICD of BV-2 cells (Fig. 1D) at 10 and 50 μM. The AICD-attenuating effect of baicalein at 10 μM was greater than that at 50 μM because of the cytotoxicity of baicalein itself. A slight cytotoxicity was observed upon treatment with 50 μM of baicalein alone (91.3 ± 2.5% viability compared with untreated control set to 100%). No significant cytotoxicity of baicalein was detected by concentrations ranging from 0.1 to 10 μM (data not shown). The inhibitory effect of 10 μM baicalein on BV-2 cell death was comparable with 0.5 mM NMMA, an NOS inhibitor (data not shown). The same pattern of microglial cell death following inflammatory activation and the inhibitory effect of baicalein was obtained by trypan blue exclusion assays (100 ng/ml LPS treatment for 48 h, 55.1 ± 2.3% cytotoxicity; 100 ng/ml LPS plus 10 μM baicalein treatment for 48 h, 23.6 ± 4.1% cytotoxicity). Treatment of BV-2 cells with either IFN-γ or LPS plus IFN-γ also induced NO production as well as cell death (Fig. 2, A and B). However, baicalein did not affect NO production or microglial cell death following treatment with IFN-γ alone, indicating that the effects of baicalein were specific for the inflammatory stimulus that activated microglia. Microglial cell death caused by the LPS treatment was due to apoptosis as determined by DNA ploidy analysis, and the reduction of cell death by baicalein was due to its anti-apoptotic effects (Fig. 2C). Apoptotic nature of LPS-induced microglial cell death has been well characterized in our previous report (including LPS time and dose responses, appearance of DNA ladder, and nuclear condensation, etc.) (Lee et al., 2001b). The inhibitory effects

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of baicalein on LPS/IFNγ-induced NO production and subsequent cell death were similarly observed in rat primary microglia cultures, indicating that the AICD-attenuating effect of baicalein is not limited to a microglial cell line (Fig. 3). Because NO production in microglia is mostly controlled by the level of iNOS expression, we next examined the effects of baicalein on iNOS induction. Baicalein at 10 and 50 μM significantly inhibited LPS-induced iNOS protein levels indicating that the inhibitory effect of baicalein on microglial NO production was due to inhibition of iNOS induction (Fig. 4).

**Baicalein Targets NF-κB to Inhibit NO-Dependent Pathway of Microglial AICD.** As the inflammatory induction of iNOS in neuroglial cells is known to be mediated mainly through NF-κB activation (Nomura, 2001), we speculated that baicalein may inhibit iNOS induction by down-regulating NF-κB activity in BV-2 cells. Gel shift assays indicated that LPS treatment of BV-2 cells strongly induced NF-κB activity, and this was inhibited by baicalein cotreatment, suggesting that the inhibition of NF-κB may be an underlying mechanism of baicalein action on iNOS induction (Fig. 5A). NF-κB-inhibiting action of baicalein was confirmed by NF-κB reporter assays (Fig. 5B). A strong antioxidant NAC also inhibited LPS-induced NF-κB reporter activity. Inhibition of NF-κB by baicalein was mainly due to the inhibition of nuclear translocation of NF-κB as demonstrated by Western blot analysis of nuclear fraction of microglial cells (Fig. 5C). To further demonstrate the involvement of NF-κB in the AICD-inhibiting action of baicalein, BV-2 cells were transiently transfected with p65 subunit of NF-κB to enhance NF-κB activity, and then the effects of baicalein on microglial AICD were assessed. Forced expression of p65 increased NF-κB activity in BV-2 cells (Fig. 5D), and this resulted in a complete abrogation of AICD-inhibiting activity of baicalein (Fig. 5E). These results suggest that baicalein inhibits microglial AICD by inhibiting NF-κB, which is re-

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**Fig. 1.** Inverse correlation between NO production and microglial cell viability upon inflammatory activation, and the effects of baicalein on microglial AICD. BV-2 cells were treated with indicated concentrations of LPS for 48 h (A) or treated with 100 ng/ml LPS for the indicated time periods (B), and then NO production or cell viability was assessed. Alternatively, BV-2 cells were treated with 100 ng/ml LPS in the presence or absence of baicalein (0.1–50 μM) for 48 h, and then NO production (C) or cell viability (D) was evaluated. Viability of untreated cells was set to 100%. The results are mean ± S.D. of three independent experiments. Asterisks (*) indicate significant differences from treatment with LPS alone (p < 0.05) (C, D).

**Fig. 2.** Specific effects of baicalein on microglial AICD. BV-2 cells were treated with LPS (100 ng/ml), IFNγ (100 units/ml), or both in the presence or absence of baicalein (10 μM) for 24 h, and then NO production or cell viability was assessed (A, B). Viability of untreated cells was set to 100%. The results are mean ± S.D. of four independent experiments. Asterisks (*) indicate significant differences between two treatments (p < 0.05). BV-2 cells treated with LPS in the presence or absence of baicalein (10 μM) for 24 h were subjected to DNA ploidy analysis (C). Numbers in histograms indicate the percentage of subdiploid cells undergoing apoptosis.
Baicalein Does Not Influence NO-Independent Microglial AICD Pathway. We next asked whether baicalein affects NO-independent apoptotic pathways. Inflammatory activation of microglia has been shown to induce caspase-11 expression followed by auto-activation of this caspase, which in turn activates downstream executioner caspases such as caspase-1 or -3 (Lee et al., 2001a). This constitutes NO-independent apoptotic pathway of activated microglia. We sought to determine whether baicalein modulates this part of microglial AICD pathways by evaluating the effects of the flavonoid on caspase-11 expression and its activity. Pretreatment of BV-2 cells with baicalein did not alter inflammatory induction of caspase-11 expression (Fig. 7A) or activity (Fig. 7B). A caspase inhibitor, z-VAD-fmk, which has been used as a control, inhibited an increase in caspase-11 activity.

The AICD-Inhibiting Effect of Baicalein Is Not Dependent on 12-Lipoxygenase Inhibition. Baicalein has been widely used as a 12-lipoxygenase inhibitor (Dailey and Imming, 1999). However, the AICD-inhibiting effect of baicalein was independent of 12-lipoxygenase inhibition, because 1) another 12-lipoxygenase inhibitor 5,8,11-eicosatriynoic acid did not exert the same inhibitory effects and 2) the product of arachidonic acid metabolism of 12-lipoxygenase, 12(S)-HETE, did not reverse the inhibitory effect of baicalein (Table 1). The 5,8,11-eicosatriynoic acid at 25 μM and 12(S)-HETE at 1 μM have been previously shown to inhibit 12-lipoxygenase (Hammarstrom, 1977) and abolish 12-lipoxygenase-inhibiting effects of baicalein (Pidgeon et al., 2002), respectively.

Discussion

In the current work, we have demonstrated that baicalein, an anti-inflammatory flavonoid derived from a Chinese medicinal herb, suppressed autoregulatory apoptosis of activated microglial cells by inhibiting NO production. The effects of baicalein were found not only in BV-2 mouse microglial cell line, but also in rat primary microglia cultures. Previous works suggested that the elimination of activated microglial cells by apoptosis could be an important mechanism whereby undesirable effects of long-term activation of microglial cells can be minimized (Lee et al., 2001b; Liu et al., 2001). Inflammatory mediators such as tumor necrosis factor α and NO that are produced by activated glial cells in CNS may have harmful effects on neurons. Inflammatory responses and their mediators may play a central role in the pathogenesis of various neurodegenerative diseases that involve chronic activation of microglial cells, such as Alzheimer's disease, Parkinson's disease, and acquired immunodeficiency syndrome-related dementia (Gonzalez-
Scarano and Baltuch, 1999). Therefore, one can speculate that the autoregulatory apoptosis mechanisms that control microglial activation may exist in vivo, and the failure of these autoregulatory mechanisms may be responsible for the deleterious effects of microglial activation. A pathophysiological importance of the regulation of microglial activation by AICD is supported by previous reports: up-regulated Bcl-xL expression has been detected in reactive microglia of patients with neurodegenerative diseases (Drache et al., 1997); and the expression of anti-apoptotic Bcl-2 protein has been associated with aged brain and neurodegenerative diseases (Migheli et al., 1994). Authors proposed that a high level of Bcl-xL or Bcl-2 protein might render microglia more resistant to cytotoxic environment, such as areas of neurodegeneration. Anti-inflammatory action of baicalein could be considered beneficial for the treatment of such neurodegenerative diseases associated with chronic inflammatory responses.

We have shown that AICD-inhibiting action of baicalein is mediated through its inhibitory effects on iNOS induction and the ensuing NO production. This NO-inhibiting effect of baicalein was based on the specific inhibition of NF-κB activity without affecting other known AICD pathways in microglia (Fig. 8). The AICD of neuroglia (microglia and astrocytes) occurs by two separate apoptotic pathways; inflammatory stimuli induce production of the autocrine toxic mediator (NO) in the IRF-1/NF-κB-dependent manner, Fig. 5. NF-κB as the major target of baicalein action. A, treatment of BV-2 cells with LPS (100 ng/ml) for 1 h induced NF-κB activation as evidenced by gel shift assays. Cotreatment of BV-2 cells with baicalein (10 μM) significantly reduced NF-κB activity. The identity of DNA-complexed proteins was confirmed by supershift assays using antibodies against p65 (p65 Ab). B, inhibition of LPS-induced NF-κB activity by baicalein was confirmed by NF-κB reporter assays. NF-κB activity was also inhibited by antioxidant NAC (10 mM) treatment. Values are fold increases in firefly luciferase activity normalized to Renilla luciferase activity after treatment with indicated stimuli for 6 h (see Materials and Methods). C, inhibition of LPS-induced NF-κB activity by baicalein was accompanied by the inhibition of nuclear translocation of p65 subunit of NF-κB as demonstrated by Western blot analysis of nuclear fraction of BV-2 cells (1 h treatment, 100 ng/ml LPS, 10 μM baicalein). Transient transfection of p65 subunit of NF-κB increased NF-κB reporter activity (D) and abolished AICD-inhibiting activity of baicalein (E). The number of blue cells expressing lacZ in untreated wells was set to 100% viability. The results are mean ± S.D. of three independent experiments. Asterisks (*) indicate significant differences between two treatments (p < 0.05).

Fig. 6. No significant effects of baicalein on NO donor-induced cytotoxicity or STAT1/IRF-1 signaling. A, BV-2 cells were treated with SNAP (0.05–1 mM) for 24 h with or without baicalein (10 μM) or z-VAD-fmk (50 μM), and then cell viability was evaluated. Viability of untreated cells was set to 100%. The results are mean ± S.D. of three independent experiments. B, after treatment of BV-2 cells with LPS (100 ng/ml) or IFNγ (100 units/ml) with or without baicalein (10 μM) for 4 h (IRF-1) or 1 h (phospho-STAT1), the levels of IRF-1 protein or phosphorylated STAT1 protein were measured by Western blot analysis. Total proteins were stained with Ponceau S to confirm an equal loading of the samples (bottom panel).

Fig. 7. No effects of baicalein on caspase-11 induction or activation. A, after 6 h treatment of BV-2 cells with LPS (100 ng/ml), IFNγ (100 units/ml), and baicalein (10 μM) as indicated, caspase-11 expression was assessed by RT-PCR. B, after treatment of BV-2 cells with LPS (100 ng/ml) in the presence or absence of baicalein (10 μM) or z-VAD-fmk (50 μM) for the indicated time period, caspase-11 activity was measured using fluorogenic substrate.
and concurrently they initiate NO-independent apoptotic pathway through caspase-11 induction (Lee et al., 2001a; Suk et al., 2002). Increased expression of caspase-11 is known to auto-activate the protease, and then activated caspase-11 is mobilized to cleave downstream caspases to initiate the apoptotic cascade (Kang et al., 2000). Meanwhile, NO seems to directly activate downstream executioner caspases (Lee et al., 2001a). Among these many players involved in the microglial AICD, NF-κB appears to be a unique target of baicalein action. Transcriptional regulation of many inflammatory genes is under control of NF-κB (Christman et al., 2000). Microglial iNOS is one of them. We have previously shown that iNOS expression is regulated by NF-κB in BV-2 microglial cells. Inhibition of NF-κB by the transfection of BV-2 cells with a super-repressor IκB mutant or antioxidants treatment led to a reduced NO production and the inhibition of AICD (Lee et al., 2001a). These results indicated that NF-κB is involved in the production of NO that acts as an autocrine mediator of apoptosis. Baicalein seems to selectively target this NF-κB activity to attenuate AICD of microglia. However, the AICD-inhibiting effect of baicalein was only partial, because of the presence of NO-independent apoptotic pathways that are not affected by baicalein (Fig. 1D). The AICD-attenuating effect of baicalein in microglia was not dependent on 12-lipoxygenase inhibition. This was supported by the following evidence: a 12-lipoxygenase inhibitor without a known antioxidant activity, eicosatriynoic acid (Hammarstrom, 1977), did not reproduce the AICD-inhibitory effect of baicalein; and the predominant product of arachidonic acid metabolism of 12-lipoxygenase, 12(S)-HETE, did not reverse the inhibitory effect of baicalein. Although baicalein has been widely used as a 12-lipoxygenase inhibitor (Dailey and Imming, 1999), many reports also demonstrated strong antioxidant and free radical scavenging effects of baicalein (Hamada et al., 1993; Gao et al., 1999; Shieh et al., 2000). Anti-oxidants are known to inhibit NF-κB activity in a variety of cell types (Christman et al., 2000), and BV-2 was not an exception (Fig. 5B). This led us to speculate that the antioxidant activity of baicalein might be responsible for the inhibition of NF-κB (and subsequent inhibition of NO production and AICD of microglia). Regardless of the relevance of 12-lipoxygenase inhibition to microglial AICD, baicalein might have inhibited 12-lipoxygenase activity in microglia under our experimental conditions. As opposed to apoptosis-inducing effects of baicalein as a 12-lipoxygenase inhibitor in many cancer cell types, baicalein up to 10 μM did not induce cell death by itself in our study. In fact, baicalein at similar concentrations previously protected neurons under various conditions by acting as an antioxidant (Gao et al., 2001; Ishige et al., 2001; Lebeau et al., 2001). This suggests that the effect of 12-lipoxygenase inhibition on cell viability depends on the cell types studied; although a variety of human cancer cells in periphery undergo apoptosis upon exposure to 12-lipoxygenase inhibitor (Dailey and Imming, 1999), neurons and neuroglia in CNS may not be affected by 12-lipoxygenase inhibition. Moreover, because baicalein has dual effects as a 12-lipoxygenase inhibitor and antioxidant, the flavonoid was able to protect microglia from AICD.

In conclusion, the plant flavonoid baicalein attenuated microglial AICD by selectively inhibiting NO-producing NF-κB activity. These effects of the flavonoid were not related to...
12-lipoxygenase inhibition. The AICD-inhibiting effect of baicalin was specific for the inflammatory stimulus in that the flavonoid blocked microglial NO production and cell death following the treatment with LPS, but not IFNγ. Our results suggest that baicalin could be a key template for the development of therapeutic agents to selectively modulate inflammatory responses and cellular apoptosis in CNS.

References
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