Baicalein is a flavonoid known to have anti-inflammatory and anti-cancer effects. In a previous study, we reported that baicalein induced hypophosphorylation of Rb, causing G1 phase arrest through activation of AhR and down-regulation of cyclin D1 and CDK4 in oral cancer cells (HSC-3). In this study, we found that in baicalein-treated HSC-3, although Rb was hypophosphorylated, the expression of p27kip, a CDK inhibitor was decreased to a level less than that in cells without baicalein treatment, which suggests that the reduction of P27kip may not be one of the causes of the hypophosphorylation of Rb. Using Western Blot to investigate how baicalein down-regulates p27kip expression, we found that baicalein treatment induced an increase in the amount of phosphorylated Akt (pAkt) at 12 and 24h. Such an increase caused an immediate corresponding reduction of the p27kip. To confirm the association of Akt pathway with the p27kip degradation, we pretreated the cells with an Akt inhibitor, MK2206, and demonstrated that the blocking of phosphorylation of Akt reversed the expression of p27kip and reduced phosphorylated p27kip (Thr187) at 12 and 24h in the baicalein-treated cells. Knowing that PI3K is an upstream signal protein of Akt, we further pretreated the cells with a PI3K inhibitor, LY294002, and demonstrated that the level of pAkt was decreased, whereas the reduction of p27kip was slightly reversed and phosphorylated p27kip (Thr187) was decreased in the baicalein-treated cells. This indicates that, in baicalein-treated HSC-3, activation of PI3K induces phosphorylation of Akt and a subsequent signaling, which in turn increases phosphorylation of p27kip (Thr187), and thereby increases the degradation of p27kip. Our data revealed that baicalein down-regulates p27kip through the PI3K-Akt pathway in oral cancer cells. Since down-regulation of p27kip is reportedly correlated with oral squamous cell carcinoma (OSCC) and its metastasis, with a poor prognosis for patients, our results suggest that baicalein’s effect on the reduction of p27kip in the oral cancer cells may have a negative effect by inducing tumor cell migration and invasion-- thus countering baicalein’s positive effect of inhibiting tumor growth (via reduction of cyclinD1 and CDK4). Further studies are urgently needed to determine the exact impact of down-regulation of p27kip on baicalein-treated cancer cells.