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Theanaphthoquinone inhibits fatty acid synthase expression in EGF-stimulated human breast cancer cells via the regulation of EGFR/ErbB-2 signaling

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Abstract

Fatty acid synthase (FAS) is a major lipogenic enzyme catalyzing the synthesis of long-chain saturated fatty acids. Most breast cancers require lipogenesis for growth. Here, we demonstrated the effects of theanaphthoquinone (TNQ), a member of the thearubigins generated by the oxidation of theaflavin (TF-1), on the expression of FAS in human breast cancer cells. TNQ was found to suppress the EGF-induced expression of FAS mRNA and FAS protein in MDA-MB-231 cells. Expression of FAS has previously been shown to be regulated by the SREBP family of transcription factors. In this study, we demonstrated that the EGF-induced nuclear translocation of SREBP-1 was blocked by TNQ. Moreover, TNQ also modulated EGF-induced ERK1/2 and Akt phosphorylation. Treatment of MDA-MB-231 cells with PI 3-kinase inhibitors, LY294002 and Wortmannin, inhibited the EGF-induced expression of FAS and nuclear translocation of SREBP-1. Treatment with TNQ inhibited EGF-induced EGFR/ErbB-2 phosphorylation and dimerization. Furthermore, treatment with kinase inhibitors of EGFR and ErbB-2 suggested that EGFR/ErbB-2 activation was involved in EGF-induced FAS expression. In constitutive FAS expression, TNQ inhibited FAS expression and Akt autophosphorylation in BT-474 cells. The PI 3-kinase inhibitors and tyrosine kinase inhibitors of EGFR and ErbB-2 also reduced constitutive FAS expression. In addition, pharmacological blockade of FAS by TNQ decreased cell viability and induced cell death in BT-474 cells. In summary, our findings suggest that TNQ modulates FAS expression by the regulation of EGFR/ErbB-2 pathways and induces cell death in breast cancer cells.

Keywords: Fatty acid synthase; Theanaphthoquinone; SREBP-1; EGFR; ErbB-2

Introduction

Breast cancer is a major cancer of women in the United States and Western Europe (Jemal et al., 2005). Early diagnosis and continuing new therapeutic approaches have managed to prevent the epidemic from causing a concomitant increase in death. Nevertheless, the death of patients due to invasive breast cancer remains a sobering fact and indicates the need to understand this disease in greater depth and to develop new interventions, both preventive and therapeutic (Medina, 2005). Overexpression of *ErbB-2* is found in approximately 30% of human breast cancers and correlates with more aggressive tumors and greater resistance to hormone therapy than ErbB-2-negative tumors (Menard et al., 2000). Activation of fatty acid synthase (FAS) expression through modulation of SREBP-1 has been reported in human breast cancer (Yang et al., 2003).

The biosynthetic enzyme fatty acid synthase (FAS) is the major enzyme required for the anabolic conversion of dietary carbohydrates to fatty acids, and it functions normally in cells with high lipid metabolism. In *de novo* lipogenesis, FAS catalyzes all reaction steps in the conversion of acetyl-CoA and malonyl-CoA to palmitate (Sul and Wang, 1998; Wakil, 1989). FAS provides proliferating cells for endogenously synthesized fatty acid for membrane phospholipid or for other functions (Pizer et al., 1996b; Jackowski et al., 2000). Therefore, a substantial subset of common human cancers – including cancers of the prostate, breast, ovary, colon, thyroid and

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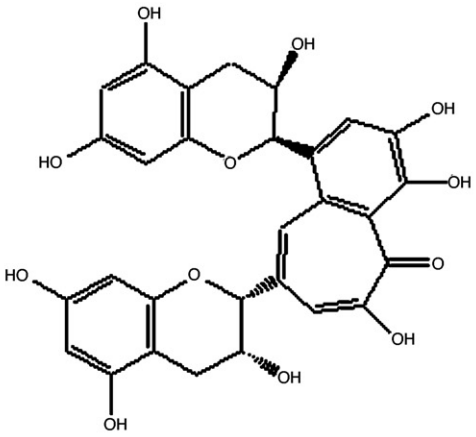
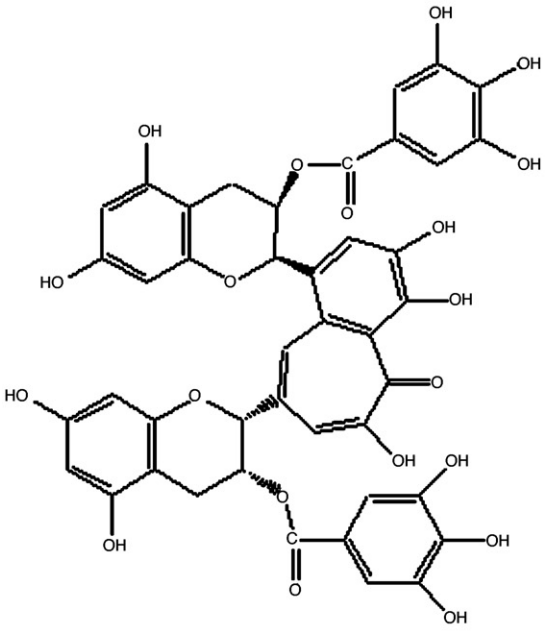
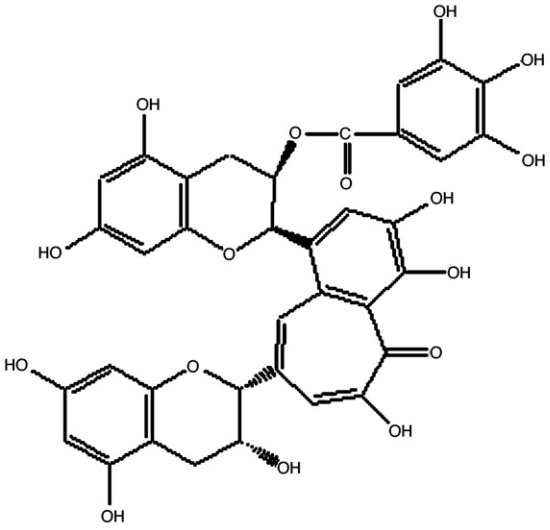


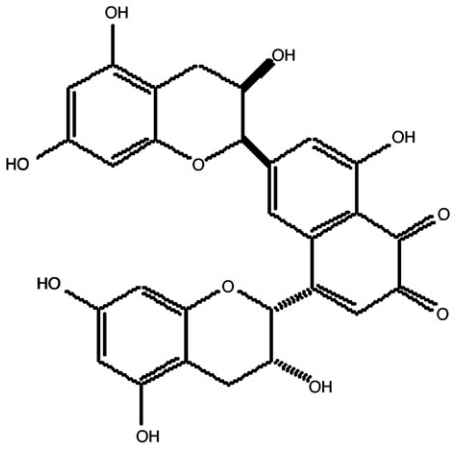
Theaflavin (TF-1)



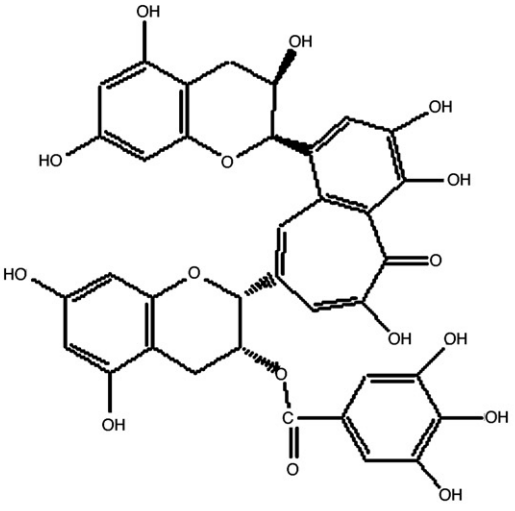
Theaflavin-3,3'-digallate (TF-3)



Theaflavin-3-gallate (TF-2a)



Theanaphthoquinone (TNQ)



Theaflavin-3'-gallate (TF-2b)

Fig. 1. Chemical structures of theaflavins and theanaphthoquinone (TNQ).