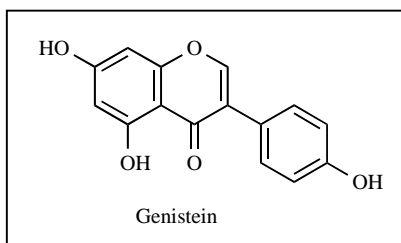


Molecule of the Month

Genistein, modest optimization of a natural product yields an increase in antioxidant activity. Oxidative stress caused by the presence of reactive oxygen metabolites (ROMs) has probably been associated with a broader range of diseases than any other cellular phenomenon. Wherever oxidative metabolism occurs ROMs will inevitably be formed, and although we have evolved extensive defense mechanisms against ROMs we cannot completely neutralize their nefarious effects. The reactivity of a ROM, such as a hydroxyl free radical, is not necessarily correlated with its toxicity. The hydroxyl free radical is extremely reactive, but not exceptionally toxic; it can cause DNA strand breaks, lipid peroxidation, and rather promiscuously oxidize many organic molecules [1]. Conversely, cyanide is not especially reactive, but is highly toxic because of its specific molecular target, cytochrome c oxidase. Without cytochrome c oxidase



a cell cannot aerobically produce ATP and will not be able to survive [1,2]. While the effect of one, large dose of cyanide on a cell is well understood the effects of the various ROMs and how they interact with our innate defense mechanisms, environment, and diet to ultimately produce a wide variety of alterations in the human condition is an area of intense, ongoing study. Superoxide is a cytotoxic ROM, and mammals possess three superoxide dismutase enzymes in order to counteract the effects of superoxide; SOD1, SOD2, and SOD3. SOD2 homozygous knockout mice develop through birth, but die within days of birth due to cardiomyopathy [1,3]. Modulating the amount of ROMs in the cell and how the cell responds to various levels of ROMs are both careful balancing acts. In general, if a cell begins to generate excessively high levels of ROMs the organism will fare better if that cell undergoes apoptosis. However, there are cases in which borderline levels of ROMs may cause irreplaceable cells to undergo apoptosis. This seems to be particularly relevant in the case of heart disease [1,3-5].

Flavonoids have been shown to have anti-cancer, anti-microbial, anti-inflammatory, and anti-apoptotic properties [5-7]. Originally, the impetus for studying flavonoids as potential therapeutics came via indirect evidence, but lately more rigorous pharmacological characterization of flavonoids has been undertaken. In January 2008 Fu and colleagues reported a library synthesis effort based on 7-difluoromethyl-5,4'-dihydroxygenistein [5]. In their library the 5 and 4' positions of 7-difluoromethyl-5,4'-dihydroxygenistein were substituted with various alkoxyates. The novel compounds were assayed for their ability to prevent apoptosis in human umbilical vein endothelial (HUVE-12) cells that were subjected to oxidative stress in the form H₂O₂

exposure. Among all of the synthesized genistein derivatives 7-difluoromethyl-5,4'-dimethoxygenistein displayed the greatest improvement in anti-apoptotic activity compared to genistein. When the HUVE-12 cells were treated with H₂O₂ (1 mM) alone about 18% of the cells underwent apoptosis; when the cells were treated with H₂O₂ (1 mM) and genistein (1 μM) about 9% of the cells underwent apoptosis; and when the cells were treated with H₂O₂ (1 mM) and 7-difluoromethyl-5,4'-dimethoxygenistein (1 μM) about 4% of the cells underwent apoptosis [5]. Fu and colleagues also showed that genistein and 7-difluoromethyl-5,4'-dimethoxygenistein both reduced apoptosis in a concentration dependent fashion; however, 7-difluoromethyl-5,4'-dimethoxygenistein is a more potent anti-apoptotic agent [5]. These data all suggest, as the authors claim, that 7-difluoromethyl-5,4'-dimethoxygenistein may protect endothelial tissue, possibly vascular endothelial tissue, against oxidative damage [5]. Further experiments in mouse models of cardiovascular disease and other diseases ought to provide interesting information on the efficacy of this natural product-derived compound. There may also be good reasons for the compounds synthesized by Fu and colleagues to be tested for efficacy in the Transgenic Adenocarcinoma Mouse Prostate model (TRAMP), as a recent paper discussed the efficacy of genistein in suppressing metastasis in the TRAMP model [6].

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