the increased synthesis of other angiogenic factors from tumor cells (Bergers and Hanahan 2008).

1.6.6 Thalidomide

Thalidomide inhibits angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), and inhibit tumor necrosis factor alpha (TNF-α) and cycloxygenase 2 (COX2), and modify the extracellular matrix (Franks *et al.,* 2004).

The main side effects of thalidomide include fatigue, constipation, nausea, vomiting, peripheral neuropathy and drowsiness (Merchant *et al.,* 2000). It has been suggested, that the teratogenic effects of thalidomide on fetal limbs may be related to inhibition of blood vessels growth in the developing fetal limb bud (Marx *et al.,* 2001). Thalidomide's anti-angiogenic effects have been demonstrated in several animal angiogenesis models and there is evidence that the drug's anti-angiogenic effects may be species specific, and possibly may be related to a species-specific metabolite and/or metabolic activation. Thalidomide reduced the area of vascularization in a rabbit corneal model of induced neovascularization (Figg *et al.,* 2001).

Thalidomide exists in two isoforms, R and S. The R isomer is hypnotic while the S isomer is responsible for the teratogenic activity (Falardeau *et al.,* 2001).

Thalidomide also inhibited angiogenesis in a rat aorta model, and in human aortic endothelial cells when human or rabbit microsomes were present, but not when rat microsomes were present (Merchant *et al.,* 2000).

The mechanism of thalidomide's anti-angiogenic effects is through the inhibition of cytokine synthesis especially that of TNF-alpha. Although some evidence from animal models showed that thalidomide's effect on angiogenesis may result from a direct inhibitory effect on some components of angiogenesis (Fife *et al.,* 1998).