In addition to block cell cycle progression, most of the endogenous angiogenesis inhibitors induces intrinsic and/or extrinsic apoptotic pathways (Sund *et al.,* 2004).

1.6.5.1.1 Angiostatin

A primary tumor could suppress its remote metastasis because expression of proangiogenic proteins within the primary tumor exceed the generation of antiangiogenic proteins resulting in the vascularization and growth of the primary tumor. However, the angiogenesis inhibitors accumulate in the circulation because of their longer half-life. Removal of the primary tumor leads to a decrease in circulating inhibitor over a period of about a week (Cao *et al.,* 1999).

The emergence of tumor angiogenesis was the result of a shift in the balance between positive and negative regulators of angiogenesis in a tumor (Rastinejad *et al.,* 1989).

Angiostatin is a polypeptide of approximately 200 amino acids. It is produced by the cleavage of plasminogen. A plasma protein that is important for dissolving blood clots. Angiostatin binds to subunits of ATP synthase exposed at the surface of the cell embedded in the plasma membrane (Cozzolino *et al.,* 1990).

1.6.5.1.2 Endostatin

Endostatin is isolated and purified from a murine hemangioendothelioma (O'Reilly *et al.,* 1997), It is a 20–22-kDa C-terminal fragment of type XVIII collagen. It was purified directly from tumor cell- conditioned medium (Bix *et al.,* 2006).

Endostatin inhibits endothelial cell proliferation and migration, induces apoptosis and causes a G1 arrest of endothelial cells (Dhanabal and Waterman *et al.,* 1999, Dhanabal and Volk *et al.,* 1999). The indirect effects on angiogenesis exerted by endostatin include inhibiting of MMP-2 activity, blocking the binding of VEGF165 and VEGF121 to VEGFR- 2, and stabilizing cell-cell and cell-matrix adhesions,