preventing the loosening of these junctions required during angiogenesis (Kim *et al.,* 2000, Kim *et al.,* 2002).

It has been demonstrated that individuals with Down's syndrome have higher levels of circulating endostatin than normal individuals due to an extra copy of the gene for the endostatin precursor on chromosome 21 (Zorick *et al.,* 2001). Interestingly, these subjects have a lower incidence of 200 different human cancers as compared with age-matched controls (Yang *et al.,* 2002). Mice engineering to genetically overexpress endostatin, mimicking individuals with Down's syndrome have slower growing tumors (Sund *et al.,* 2005).

Endostatin, an angiogenesis inhibitor produced by hemangioendothelioma. Endostatin specifically inhibits endothelial cell proliferation, increase apoptosis in malignant cells, and potently inhibits angiogenesis and tumor growth (O'Reilly *et al.,* 1997). Endostatin is derived from E.coli.

While some cancer therapies may develop a resistance to further treatment, endostatin and angiostatin do not appear to cause a buildup of drug resistance, indicating they could be used whenever needed (Herbst *et al.,* 2002).

1.6.5.2 Drugs that block endothelial cell proliferation

Several endogenous angiogenesis inducers have been described which cooperate to tightly regulate the processes of endothelial cell migration, proliferation and differentiation (Nicholas *et al.,* 2006).

The first class of molecules specifically targets endothelial cells and includes members of the VEGF family and angiopoietins (Frederick *et al.,* 2000).

The second group consists of factors such as cytokines, chemokines and enzymes, such as fibroblast growth factor-2 (bFGF-2), which activate cells other than endothelial cells (Katanasaka *et al.,* 2008).