CV247 Components

CV247 – POSSIBLE MODUS OPERANDI OF THE COMPONENTS

The mode of action of the components of CV 247 is summarised as follows:

Manganese (Mn)

In both animals and man, Mn is an essential trace element for normal brain functioning and for many ubiquitous enzymatic reactions, including hexokinase, superoxide dismutase and xanthine oxidase. Superoxide dismutases (SODs), are part of the defence mechanism against reactive oxygen species, and altered amounts of copper/zinc SOD and MnSOD have been implicated in multistage carcinogenesis in both rodents and man (Davis, 1999).

The catalytic reaction of SOD in detoxifying superoxide involves a redox reaction that utilises either copper (cytosolic and extracellular Cu/Zn SODs) or Mn (mitochondrial MnSOD). In the active site of the SOD enzymes, Cu or Mn is alternatively reduced or oxidised by superoxide to produce hydrogen peroxide (which is then further metabolised by either catalase or glutathione peroxidase). MnSOD within animal tumours has been reported to be low (Markland,1982), and since both low Cu/ZnSOD and MnSOD have been reported to be associated with cancer susceptibility (Finley and Davis, 1999), the need to maintain adequate levels of Mn is important.

Studies have shown that even marginal trace element deprivation, including Cu and Mn, can significantly alter immunologic function and have been shown to affect the initiation and progression of a large variety of neoplasia.

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Copper (Cu)

Copper, like manganese and zinc, is chemically classified as a transitional element in the periodic table. It's essential role in animals and man was first realised in 1926 after it was found to be required for haemaglobin synthesis in rats (Mann, 2000).

Copper can form complexes in which the metal serves as a central atom and as a result its function is closely associated with its binding to biological ligands, particularly in enzyme systems. Like manganese, Cu can adopt distinct redox states allowing the metal to play a pivotal role in cell physiology as a catalytic co-factor in the redox chemistry of enzymes, mitochondrial respiration, iron absorption, free radical scavenging and elastin cross-linking.

The importance of Cu can be attributed to its role as a co-factor in a number of enzymes that are involved in the defence against oxidative stress, and a deficiency compromises the anti-oxidant defence system of cells thus increasing their susceptibility to oxidative DNA damage (Pan, 2000). Copper containing superoxide dismutase (Cu/ZnSOD) has been found to be lower in malignant cell lines as compared to normal tissues (Marklund,1982), and reduced amounts of copper/zinc SOD and MnSOD have been implicated in multistage carcinogenesis in both rodents and man (Davis, 1999). Copper loading of rats has been shown to increase both liver cytosol and mitochondrial SOD activity (Russanov, 1986). Copper gluconate has been claimed to have tumour inhibiting properties and has been used in high doses for the treatment of cancer tumours (Nieper, 1979).

Copper deficiency is known to impair immune function as a consequence of reduced production of both neutrophils and T lymphocytes. Copper deficiency is also known to inhibit the proliferation of T cells in response to mitogens (Stipanouk, 2000).

Vitamin C

Vitamin C (ascorbic acid) is regarded as the most important anti-oxidant in mammalian cells. With the exception of primates, it is synthesised in animals from D-glucose or D-galactose via the glucuronic acid pathway.

As a strong reducing agent, vitamin C forms a part of the body's antioxidant defences against reactive oxygen species (ROS) and free radicals, possibly by preventing the inhibition of gap junction intercellular communication, which is known to be induced by hyrogen peroxide.

Oxidative stress, whether from an increased production of oxidants or from a failure of physiological anti-oxidant systems, can cause cancer (Bjelakovic, 2004), and consequently the use of anti-oxidant supplements is widespread. Ascorbic acid is the single nutrient supplement most commonly used by cancer patients (Block, 2003).

Cells involved in the immune response normally contain very high concentrations of vitamin C. Aging and chronic disorders, such as cancer, are associated with depression of immunity and are accompanied by depleted levels of both plasma and leucocyte vitamin C (Basu, 1996). Proposed mechanisms of action for ascorbic acid in the prevention and treatment of cancer include enhancement of the immune system (Head, 1998); notably it may promote chemotaxis, reduce allergic reactions and raise interferon production (Anderson, 1981). In addition because vitamin C is

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involved in the mechanism which enables DNA to “sense” free radicals by integrating with the iron embedded in DNA, it may facilitate DNA repair and is therefore an important factor in immune surveillance against cancer (Fragu, 1991).

Numerous, albeit uncontrolled, epidemiological studies in man, have pointed to the importance of both dietary and supplementary ascorbic acid in the prevention of various types of cancer including bladder, breast, cervical, colorectal, oesophageal, lung, pancreatic, prostate, salivary gland, stomach. leukaemia and non-Hodgkins lymphoma (Head, 1998).

Sodium salicylate (SS)

Sodium salicylate is a well documented and widely monographed, non-steroidal anti-inflammatory drug m(NSAID).There is much current interest in the NSAIDs as possible chemotherapeutic agents.

Though SS and other NSAIDs maybe able to act independently of cyclo-oxygenase (COX) activity and prostaglandin synthesis activity (Tegeder, 2001), the salicylates, in general, are known to be able to exert an anti-inflammatory effect, by direct blocking of prostanoid synthesis from arachidonic acid, and by virtue of their inhibition of the COX enzymes. COX 2, in particular, is induced in response to cell activation by pro-inflammatory cytokines, growth factors and tumour promoters, and thus may have a pathophysiological role connected to inflammation and carcinogenesis.

It has been demonstrated that elevated levels of PGE2 are synthesised in tumour cells over-expressing COX-2, which results in secretion of VEGF, TGFβ and others to induce angiogenesis. PGE2 also has several inhibitory effects on lymphocytes, including suppressing lymphokine-activated killer cells and cell-cell mediated tumour cell killing.

Thus COX 2 or PGE2 inhibition would be anti-angiogenic, and could stimulate anti-tumour immuno-surveillance (Simmons, 2001). Though salicylates have been reported to be only weak inhibitors of both isolated COX 1 and COX 2, they are potent inhibitors of prostaglandin (PG) synthesis in intact cells, and salicylate, or its metabolites, may selectively inhibit PGE2 synthesis (Graham, 2003).

The COX 2 tumour hypothesis has been supported by various experimental animal models but does not preclude the role of other factors, such as the role that COX 1 plays in carcinogenesis, and the fact that SS prevents nuclear factor kappa B activation and hence can cause tumour cell apoptosis (Wu, 2001).