Why Elephants Rarely Get Cancer: 40 Genes that Code for the p53 Tumor Protein!

Dr. Joshua Schiffman and his colleagues from the Huntsman Cancer Institute (HCI) at the University of Utah and Arizona State University, have studied why elephants rarely get cancer.

The answer partially lies in the p53 tumor protein, also known as the p53 tumor suppressor gene. This protein prevents cancer formation and functions as a tumor suppressor. The p53 tumor suppressor gene has been described as “the guardian of the genome” due to its ability to prevent genome mutation.
The elephant genome has 40 copies (alleles) of genes that code for the p53 tumor suppressor gene, which is 38 more than humans.
Humans have 2 genes that code for the p53 protein. The “extra” p53 proteins has explained why elephant’s have enhanced resistance to cancer.  

In humans, the cancer mortality rate is approximately 11 to 25 percent. However, in elephants, this mortality rate is 5 percent, despite the fact that elephants can weigh about 10,500 lbs. (4,800 kilograms) and live for up to 65 years.

The majority of the p53 genes in elephants are so-called retrogenes, which are modified duplicates developed over time through evolution of the species.

The p53 protein in humans, in particular, has many mechanisms of anticancer function, such as:

- Inhibition of angiogenesis (Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels)
- Activates DNA repair proteins when DNA has sustained damage
- Arrests growth by holding the cell cycle at the G1/S regulation point on DNA damage recognition
- Initiates apoptosis (i.e., programmed cell death)

Mutations in the p53 protein can result is carcinogenesis. It has been concluded that Aflatoxin, the fungal carcinogen first identified in 1960, is now recognized as the prototypical laboratory carcinogen. It causes mutations in the p53 tumor-suppressor gene as well as ras mutations, which are involved in the majority of human cancers.

It is important to continuously up-regulate and enhance the p53 tumor suppressor gene in humans. There are certain natural substances identified that are known to up-regulate and enhance the p53 tumor suppressor gene. They are listed in the Table below:

### Natural Substances that Up-Regulate and Enhance p53 Tumor Suppressor Gene
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<tr>
<th>Substance</th>
<th>Abstract of Study</th>
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<td>Inositol hexaphosphate (InsP6 or IP6)</td>
<td>These data demonstrate that IP6 up-regulates the expression of the tumor suppressor gene p53 and p21WAF1/CIP1 gene and their modulation may be one of the mechanisms of the anti-neoplastic action of IP6. Since loss of p53 function enhances cancer cells' resistance to chemotherapeutic agents, the stimulating function of IP6 on p53 makes it an attractive adjuvant chemotherapeutic agent as well.</td>
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<td>Ellagic Acid</td>
<td>The effects of ellagic acid on cell cycle events and apoptosis were studied in cervical carcinoma (CaSki) cells. We found that ellagic acid at a concentration of 10(-5) M induced G arrest within 48 h, inhibited overall cell growth and induced apoptosis in CaSki cells after 72 h of treatment. Activation of the cdk inhibitory protein p21 by ellagic acid suggests a role for ellagic acid in cell cycle regulation of cancer cells.</td>
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<td>Apigenin (topically applied)</td>
<td>The mechanism of p53 protein stabilization is currently being investigated. To determine whether p53 was transcriptionally active, we also performed gel mobility shift assays and transient transfection studies using a luciferase plasmid under the control of the p21/waf1 promoter. Both p53 DNA-binding activity and transcriptional activation peaked after 24 h of exposure to apigenin. These studies suggest that apigenin may exert anti-tumorigenic activity by stimulating the p53-p21/waf1 response pathway.</td>
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<td><strong>P5 Tumor Suppressor Gene</strong></td>
<td>Our data indicate that folate deficiency induces DNA strand breaks and hypomethylation within the p53 gene. Such alterations either did not occur or were chronologically delayed when examined on a genome-wide basis, indicating some selectivity for the exons examined within the p53 gene. Folate insufficiency has been implicated in the development of several human and experimental cancers, and aberrations within these regions of the p53 gene that were examined in this study are thought to play an integral role in carcinogenesis. The aforementioned molecular alterations may therefore be a means by which dietary folate deficiency enhances carcinogenesis.</td>
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<td><strong>Folate (Folic acid)</strong></td>
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<td>P5 Tumor Suppressor Gene</td>
<td>We observed that p53 was highly expressed in HT-29 cells and curcumin could up-regulate the serine phosphorylation of p53 in a time- and concentration-dependent manner. An increase in expression of the pro-apoptotic factor Bax and a decrease in expression of the anti-apoptotic factor Bcl-2 were also observed in a time-dependent manner after exposure of 50 microM curcumin, while the expression of the anti-apoptotic factor Bcl-xL was unchanged. Curcumin could also down-regulate the expression of pro-caspase-3 and pro-caspase-9 in a time-dependent manner. These data suggest a possible underlying molecular mechanism whereby curcumin could induce the apoptosis signaling pathway in human HT-29 colon adenocarcinoma cells by p53 activation and by the regulation of apoptosis-related proteins. This property of curcumin suggests that it could have a possible therapeutic potential in colon adenocarcinoma patients.</td>
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Informational References:

Video – Dr. Schiffman and the elephants who inspired him

Resources:

- **Curcumin**
- **Ellagic Acid**
- **Folate (as Methyl Folate)**
Inositol hexaphosphate (InsP6 or IP6)

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- Triterpenoid Saponins From Plants Show Potential As Chemopreventive Agents
- Consume The 4 Glucosinolate Rich Foods To Produce The 4 Isothiocyanates In Order To Reduce the Risk Of Cancer