

**Multiple effects of anthocyanins inhibiting influenza (flu) virus infectivity, decreasing secondary tissue damage and boosting the immune system:  
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**How important are anthocyanins in human ability to fight viral infections?** The answer to this question has two parts. The first part is clear. Diet rich in polyphenols including anthocyanins helps the human immune system to work more efficiently to protect against viral infections. The second part is a little bit more complex, specific types of anthocyanins may have a direct effect in **decreasing influenza viruses infectivity** by decreasing the ability of the virus itself to get into the human cells [1-3] or to be released from infected cells [4]; or by having a **viricide effect [4-7]**, it means that some anthocyanins may kill viruses when they are in the lumen of the respiratory or intestinal tract. From this perspective, anthocyanins are very helpful in our battle against influenza.

**Does it mean that anthocyanins can prevent influenza virus infections?** That is not the case; the only way to develop permanent immunity to a given virus is by allowing the immune system to fully respond to it (after exposition to the virus or to some antigenic vaccines). However, increasing evidence suggests that anthocyanins may help by modulating the efficiency of the immune response in such a way that severity of symptoms and tissue damage may be substantially decreased. This characteristic gets more importance in the light of the increased risk of epidemic spread of new, deadly strains of influenza virus as in the case of the bird flu and the swine flu.

**Why some people suffer milder forms of the disease, while others die despite being infected for the same viral strain and despite having similar treatment?** There are some obvious reasons for this, like the genetic background, immunization and the overall nutritional state. However, there are two additional factors: **viral load related to the number of viral particles present at a given time in tissue or fluids; and secondary tissue damage [8-10] characterized by the death of cells that are not infected with the virus yet: this includes at least three aggravating factors, release of free radicals (ROS) and toxic mediators from dying cells infected with the virus; release of ROS and inflammatory (by activation of the pro-inflammatory NfκB signaling pathway, by inducing airway hyperreactivity, and by gating apoptosis mediated by mitochondrial DNA oxidative damage) mediators by immune cells, and side effects of antiviral medication[11-16]**. Both of these factors are modified by mechanisms that were described above to be associated with the therapeutic effects of anthocyanins. As example, In the immune system anthocyanins induce macrophages to secrete tumor necrosis factor alpha (TNFα) [17, 18], TNFα has a strong viricide effect [19] decreasing influenza viral counts up to 28% in cultures of kidney cells [17]. Similarly, polyphenols neutralize influenza A virus directly in culture [4, 20, 21], and inhibit viral adhesion to cell membrane receptors *in vitro* [1, 3] without affecting cell viability [2]. Unfortunately, only few clinical studies showing the importance of anthocyanins in influenza treatment and prevention have been performed [22, 23], just enough to put in evidence the need for additional research studies. However, extensive research *in vitro* [4, 24] and in animal models *in vivo* [25], constitutes demonstration of anthocyanins-mediated antiviral effects; which is of particular importance if it is noted that the antiviral effect of polyphenols is not significantly affected by viral mutations because they are binding to the viral envelope lipids or sugar moieties [6].

**How much is an adequate, therapeutically effective doses of anthocyanins?** There is clear justification to consider anthocyanins in the treatment and prevention of the flu (specially having into account that in case of an epidemic outbreak, it may be potentially difficult and stressing to

get the formal antiviral treatment from the health system; no antiviral medication is 100% effective, and viral responses to medications change over time). However, although not toxicity has been reported with anthocyanins, it is not clear the amount of them required. Medox™ is a presentation of anthocyanins with the highest (80mg), standardized concentration of anthocyanins available (and includes additional 115mg of other polyphenols). Anthocyanins have been shown to help in the seasonal flu [23], and are a good alternative to complement other measurements; including diet, since this amount of anthocyanins and polyphenols (equivalent to the amount contained in Medox™) would imply daily consumption of many pounds of a combination of anthocyanins-containing fruits and vegetables.

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