

# Could This Common Supplement Be the Answer to Tumors?

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## STORY AT-A-GLANCE

- › NAC restores the sensitivity of drug-resistant breast cancer cells to treatment, according to researchers with the Department of Biomedicine of the University of Basel in Switzerland
- › NAC unexpectedly even increased alpelisib's effectiveness in previously resistant cancer cells
- › NAC has the potential to prevent DNA damage, cancer and other mutation-related diseases via inhibition of invasion and metastasis, effects in mitochondria and more
- › Another study found NAC inhibits the growth, adhesion, migration and invasion of human bladder cancer cells
- › Beyond its role as a cancer fighter, NAC may help ward off premature aging and offers benefits for neurological health, stroke, COVID-19 and more

**N-acetylcysteine (NAC), a precursor for glutathione biosynthesis, is a common dietary supplement that could hold a secret to treating tumors resistant to conventional cancer drugs. Researchers with the Department of Biomedicine of the University of Basel in Switzerland, found NAC restores the sensitivity of breast cancer cells to treatment.<sup>1</sup>**

**NAC is already valued in the medical field for helping increase glutathione in the body, which prevents liver damage in cases of acetaminophen (Tylenol) overdose. It also reduces acetaldehyde toxicity,<sup>2</sup> which causes many hangover symptoms. But, it seems,**

NAC is living up to its reputation as an “old drug with new tricks,” as the featured study suggests it may significantly improve treatment of advanced breast cancer.

## **NAC May Help Fight Resistant Breast Cancer**

Breast cancer is the most common cancer in women, with more than 2.2 million cases developing annually.<sup>3</sup> Among women with recurring disease, survival rates have barely improved in the last two decades. “Most recurring metastatic cancers are either drug resistant or will become resistant to therapy,” researchers wrote in *Cell Reports Medicine*. “Thus, drug resistance is a substantial hurdle in the long-lasting cure of patients.”<sup>4</sup>

About 70% of breast cancers have mutations in genes that affect the PI3K signaling pathway.<sup>5</sup> The overactivation of PI3K promotes tumor development, which is why the drug alpelisib (brand name Piqray) — a PI3K $\alpha$ -selective inhibitor — is often used to treat it. Resistance to the drug, however, is a serious problem.

“Unfortunately, it turned out that the success of the medication is severely limited by resistance,” researcher Mohamed Bentires-Alj said in a University of Basel news release. “Hence, we urgently need to find out more about how resistance arises.”<sup>6</sup>

The team found mutations that turn off production of a protein called NF1, which suppresses tumor growth, were involved in cancers resistant to alpelisib. “The absence of NF1 is the elephant in the room; it throws everything into disarray within the cell and hinders successful treatment,” Bentires-Alj said.<sup>7</sup>

With NF1 lost, the team found cells produce less energy via their mitochondria and rely more on other energy production pathways. NAC, an antioxidant, affects energy metabolism similarly, so the researchers expected it would have similar effects in cancer cells as NF1 loss. Instead, the opposite happened.

NAC unexpectedly restored — and increased — alpelisib’s effectiveness in previously resistant cancer cells. NF1 loss is also often involved in other cases of drug resistance,

including in skin, ovarian, endometrial, lung and bladder cancers, so it's possible NAC could be useful for treatment of multiple drug-resistant cancers.<sup>8</sup>

"As N-acetylcysteine is a safe and widespread additive, this result is highly relevant for clinical research," says Bentires-Alj. The team plans to conduct further trials in breast cancer patients to see if NAC improves treatment of resistant cases.<sup>9</sup> The study concluded:<sup>10</sup>

*"NF1 loss is a resistance-enhancing event in PI3K $\alpha$  inhibition. This suggests that patients with tumors lacking NF1 are likely to develop resistance to PI3K $\alpha$  inhibition. Furthermore, we discovered that NAC treatment circumvents resistance to PI3K $\alpha$  inhibition, likely by dampening glycolytic activity and mTOR signaling, and may be an attractive strategy to be tested in patients with NF1 loss-evoked resistance."*

## NAC's Anticancer Effects

NAC, a form of the amino acid cysteine, has long been regarded as a preventive and therapeutic tool in conditions that involve glutathione depletion. It's been found to be safe "even at very high doses and for long-term treatments," according to University of Genoa researchers in a Carcinogenesis review.<sup>11</sup>

The study pointed out that NAC has the potential to prevent DNA damage, cancer and other mutation-related diseases, noting its "impressive array of mechanisms and protective effects towards DNA damage and carcinogenesis." This includes:<sup>12</sup>

Nucleophilicity	Antioxidant activity	Modulation of metabolism
Effects in mitochondria	Decrease of the biologically effective dose of carcinogens	Modulation of DNA repair

Inhibition of genotoxicity and cell transformation	Modulation of gene expression and signal transduction pathways	Regulation of cell survival and apoptosis
Anti-inflammatory activity	Anti-angiogenetic activity	Immunological effects
Inhibition of progression to malignancy	Influence on cell cycle progression	Inhibition of preneoplastic and neoplastic lesions
Inhibition of invasion and metastasis	Protection toward adverse effects of other chemopreventive agents or chemotherapeutical agents	

A number of studies support NAC's anticancer potential. In a study on mice, the combination of a ketogenic with NAC significantly reduced tumor growth in anaplastic thyroid cancer, an aggressive and often deadly form of the disease.<sup>13</sup> Another study found NAC inhibits the growth, adhesion, migration and invasion of human bladder cancer cells.<sup>14</sup>

Similar effects have been observed in breast cancer cells, with NAC reducing proliferation and increasing apoptosis, or cell death.<sup>15</sup> When combined with bromelain, NAC also significantly inhibited proliferation and survival of gastrointestinal cancer cells.<sup>16</sup>

## Is NAC a Fountain of Youth?

Beyond its role as a cancer fighter, NAC may help ward off premature aging with its longevity-enhancing effects. Specifically, a combination of NAC and glycine, known as GlyNAC, improved "deficits associated with premature aging" in people with HIV.<sup>17</sup> This included improvements to oxidative stress, mitochondrial dysfunction, inflammation, endothelial dysfunction, insulin resistance, genotoxicity, strength and cognition.<sup>18</sup>

A subsequent pilot trial in older humans found similar results, with GlyNAC supplementation for 24 weeks correcting glutathione deficiency and improving multiple measures of health, including:<sup>19</sup>

Mitochondrial dysfunction	Oxidative stress	Inflammation
Endothelial dysfunction	Insulin resistance	Genomic damage
Cognition	Strength	Gait speed
Exercise capacity	Body fat levels	Waist circumference

The researchers concluded, “Supplementing GlyNAC in aging humans could be a simple and viable method to promote health and warrants additional investigation.”<sup>20</sup> GlyNAC supplementation also improved four of nine hallmarks of aging known to contribute to age-related disorders. This includes:<sup>21</sup>

1. Mitochondrial dysfunction
2. Inflammation
3. Insulin resistance
4. Genomic damage

## **NAC’s Neuroprotective Effects and Stroke Benefits**

People with hereditary cystatin C amyloid angiopathy (HCCAA), a rare genetic disorder,<sup>22</sup> have an average life expectancy of just 30 years, and most die within five years of their first stroke,<sup>23</sup> so reducing their incidence could prove to be essential to increasing survival.

NAC may help prevent strokes in the population by preventing the formation of amyloid-producing proteins, which promote amyloid deposits linked to strokes.<sup>24</sup>

Researchers from Children's Hospital of Philadelphia (CHOP) conducted the study, noting NAC could also have potential for Alzheimer's disease because the process of protein deposition that occurs in HCCAA is similar to what occurs in Alzheimer's, although at an accelerated pace in HCCAA.

## **NAC Shows Promise for Psychiatric and Neurological Disorders**

NAC also shows particular promise in the treatment of mental health disorders, including post-traumatic stress disorder,<sup>25</sup> depression<sup>26</sup> and substance use disorders.<sup>27</sup>

It's known to modulate pathophysiological processes – such as oxidative stress, neuroinflammation and dysregulation of glutamate and dopamine neurotransmitter systems – that contribute to psychiatric and neurological disorders.<sup>28</sup> According to a systematic review published in *Neuroscience & Behavioral Reviews*:<sup>29</sup>

*“In this systematic review we find favorable evidence for the use of NAC in several psychiatric and neurological disorders, particularly autism, Alzheimer's disease, cocaine and cannabis addiction, bipolar disorder, depression, trichotillomania, nail biting, skin picking, obsessive-compulsive disorder, schizophrenia, drug-induced neuropathy and progressive myoclonic epilepsy.*

*Disorders such as anxiety, attention deficit hyperactivity disorder and mild traumatic brain injury have preliminary evidence and require larger confirmatory studies ... Overall, NAC treatment appears to be safe and tolerable.”*

## **Was NAC Targeted Because It Fights COVID-19?**

Among NAC's many benefits is the ability to reduce viral replication of certain viruses, including the influenza virus.<sup>30</sup> During the pandemic, NAC emerged as a **tool for preventing and treating COVID-19**, including the hypercoagulation that can result in stroke and/or blood clots<sup>31</sup> that impair the ability to exchange oxygen in the lungs. As noted in the *FASEB Journal* in 2020:<sup>32</sup>

*“Based on a broad range of antioxidant and anti-inflammatory mechanisms ... the oral administration of NAC is likely to attenuate the risk of developing COVID-19, as it was previously demonstrated for influenza and influenza-like illnesses.*

*Moreover, high-dose intravenous NAC may be expected to play an adjuvant role in the treatment of severe COVID-19 cases and in the control of its lethal complications ... including pulmonary and cardiovascular adverse events.”*

Another literature analysis<sup>33</sup> concluded glutathione deficiency may be associated with COVID-19 severity, leading the author to conclude that NAC may be useful both for its prevention and treatment.

Not long after several scientists had called attention to NAC’s benefits against COVID, the U.S. Food and Drug Administration (FDA) suddenly cracked down on the supplement, claiming it was excluded from the definition of a dietary supplement because it was approved as a new drug in 1963<sup>34</sup> — before it was marketed as a dietary supplement or as a food.

Retailers, including Amazon, pulled supplements containing NAC from their shelves in response, as the FDA’s move meant NAC could no longer legally be marketed as a supplement, even though there were no fewer than 1,170 NAC-containing products in the National Institutes of Health’s Dietary Supplement Label Database at the time.<sup>35</sup>

Draft guidance released by the FDA in April 2022,<sup>36</sup> however, included verbiage suggesting the FDA would not be enforcing their policy that NAC cannot be marketed as a dietary supplement, even though it was technically still illegal to do so. In August 2022, following the FDA’s release of its final guidance, Amazon “quietly notified” supplement makers that it was resuming the sale of NAC dietary supplements.<sup>37</sup>

Fortunately, research into NAC’s potential anticancer and other disease-reducing effects is ongoing. And if you’re intrigued by NAC’s health-boosting potential and are interested in supplementing with NAC, it’s inexpensive and, for now, widely available.

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