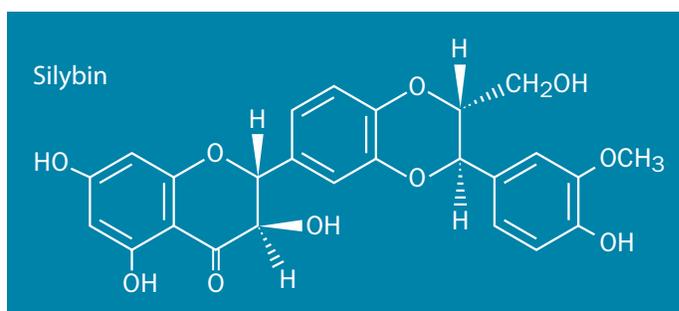


Silybin-Phosphatidylcholine Complex

Introduction

The fruit of the milk thistle plant (*Silybum marianum*, family Asteraceae/Compositae) has been a liver support remedy for 2,000 years.¹ The standardized extract known as silymarin contains three flavonoids of the flavonol subclass. Silybin predominates, followed by silydianin and silychristin. Silybin is



an effective antioxidant, conserving glutathione (GSH) in liver cells while stabilizing the liver cell membranes against oxidative attack.¹ Animal experiments have shown silybin blocks the oxidative toxicities of acetaminophen, alcohol, carbon tetrachloride, and the mushroom toxins phalloidin and alpha-amanitin.²⁻⁴ These findings correlate with decades of clinical observations that silybin improves survival after ingestion of deathcap mushrooms (*Amanita* species).⁵ Although silybin is the most potent of the flavonoids in milk thistle, like other flavonoids it is not well-absorbed. The utilization of non-phytosome silybin intravenously in mushroom-toxic patients (at 20-50 mg/kg/day) or of high-dose silymarin at 600 mg/day in diabetic patients has resulted in meaningful symptom improvement,⁶ presumably because the preparations were given either intravenously or at high oral doses. However, silybin-phosphatidylcholine complexed as a phytosome provides significant liver protection and enhanced bioavailability over conventional silymarin.

Biochemistry

Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed.⁷ The poor absorption of flavonoid nutrients is likely due to two factors. First, they are multiple-ring molecules too large to be absorbed by simple diffusion, while they are not absorbed actively, as occurs with some vitamins and minerals. Second, because flavonoid molecules typically have poor miscibility with oils and other lipids, they are severely limited in their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine.

Water-soluble flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called phytosomes. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood.⁸ Lipid-phase substances employed to make flavonoids lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). PC, the principal molecular building block of cell membranes, is miscible both in water and in oil/lipid environments and is well absorbed when taken by mouth. Precise chemical analysis indicates a phytosome is usually a flavonoid molecule linked with at least one PC molecule. A bond is formed between the two molecules, creating a hybrid molecule. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte's outer cell membrane.

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Phosphatidylcholine is not merely a passive “carrier” for the bioactive flavonoids of the phytosomes, but is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis.⁹ The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial PC intakes.¹⁰

Phytosomes are not liposomes; structurally, the two are distinctly different. The phytosome is a unit of several molecules bonded together, while the liposome is an aggregate of many phospholipid molecules that can enclose active phytomolecules, but without specifically bonding to them.¹⁰ See Kidd for a more complete review of phytosomes.¹⁰

Pharmacokinetics

The animal and human pharmacokinetics of the silybin phytosome complex have been reviewed in depth.¹¹ With respect to bioavailability, it is the most thoroughly researched of the existing phytosome preparations. For equal quantities of silybin taken by mouth, the phytosome form achieves markedly higher plasma levels of silybin than does the conventional, non-phytosome form.

The comparative uptakes of silybin from the phytosome form versus the non-phytosome form were investigated in two human studies. In the first, young healthy subjects (ages 16-26, n=8) took single 360-mg doses of silybin by mouth, either as the phytosome or as conventional silybin.¹² After eight hours the plasma silybin level achieved from the phytosome was almost three times that of the non-complexed silybin. By measuring the total area under the curve (AUC), it was determined that silybin is absorbed almost five times better from its phytosome than its conventional form.

The second human pharmacokinetic study was conducted with the same healthy young volunteers.¹² In this study, rather than a single dose of 360 mg, the silybin dose was 240 mg daily (120 mg every 12 hours) for eight days. This pattern of daily intake achieved high plasma concentrations and high total absorption on the

eighth day, matching those attained by the single higher dose (360 mg) given for one day, indicating no apparent decline in absorption efficiency after multiple days of intake.

Beyond improved delivery of silybin into the circulation, the silybin phytosome more capably delivers silybin to the liver. This was demonstrated by collecting bile secreted from the working livers of nine patients who had earlier undergone surgical gallbladder removal (necessitated by gallstones); thus, the patients were already equipped for bile collection.¹³ They were given single oral doses of 120 mg silybin, either as silybin phytosome or conventional silymarin. Bile collected over 48 hours contained 11 percent of the total dose of silybin from the phytosome form, compared to three percent from the non-complexed silybin source. In this study the plasma silybin level from the conventional silymarin dosing was almost undetectable, suggesting a 120-mg oral dose of silybin as silymarin may not be clinically effective.



Silybin collected in the bile is a valid measure of silybin that has traversed the liver tissue. Therefore, these data suggest the human liver receives about a four-fold higher exposure to silybin coming from phytosomes than from non-complexed silymarin.¹² The bile clearance data also are consistent with silybin's 4.6-times greater plasma bioavailability from intestinal absorption.¹²

In another study by the same group,¹⁴ 14 volunteers with cholestasis took only the silybin phytosome (120 mg silybin orally as a single dose) and showed rapid and substantial plasma absorption of silybin that peaked at 3-4 hours. Probably because the subjects were not secreting silybin into bile, relatively high levels persisted in the plasma up to 24 hours.

Mechanisms of Action

The liver is exceptionally vulnerable to toxic attack as hepatocytes continually sort, separate, metabolize, or store a variety of substances that reach the liver directly following absorption into the blood. Some,

such as triglycerides and fat-soluble vitamins, are packaged by the hepatocytes into lipoprotein particles and dispatched to other tissues. Others pose a toxic threat until they can be detoxified. The liver's position immediately "downstream" from the intestine puts it at risk from food-borne toxic agents. In addition to food-borne toxins, such as herbicide and pesticide residues, artificial preservatives, and other synthetic food additives, the liver must deal with other toxins that enter the body via diverse routes. These can include alcohol, cigarette-smoke toxins, street drugs, viral and bacterial antigens, heavy metals, solvent pollutants, and over-the-counter and prescription pharmaceuticals. During the detoxification process, glutathione, the key antioxidant in the liver's parenchymal cells, is directly or indirectly consumed.¹⁵

The antioxidant capacity of silymarin's flavonoids substantially boosts the liver's resistance to toxic insults.¹⁶ It is now known that silybin is the most potent of the three flavonoids in silymarin.⁴ Silybin has been extensively researched and found to have impressive bioactivity, albeit limited by poor bioavailability. In its native form within the milk thistle fruit, silybin occurs primarily complexed with sugars, as a flavonyl glycoside or flavonolignan. As a silybin-phosphatidylcholine complex, silybin protects the liver by conserving glutathione in the parenchymal cells, while PC helps repair and replace cell membranes.¹⁷ These constituents likely offer the synergistic benefit of sparing liver cells from destruction.

Clinical Indications

The silybin phytosome complex demonstrates better results for lowering liver enzymes, albeit in relatively small clinical trials.^{11,18-23} The phytosome form has produced degrees of symptomatic improvement in clinical trials of liver cirrhosis and alcoholic, iatrogenic, and viral hepatitis (types A, B, and C).¹⁸⁻²³ Taken altogether, the trial data suggest liver damage indicators in patients with acute or chronic hepatitis B and/or C will respond to 800-1,600 mg/day of silybin-phosphatidylcholine (providing 240-480 mg/day silybin) over 7-120 days.^{19,20,22,23}

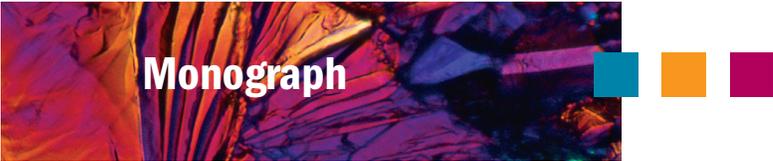
Hepatitis

Findings from human studies indicate oral silybin as Siliphos[®] has markedly greater benefit, milligram for milligram, than does non-complexed silybin from silymarin.

In 1991, Marena and Lampertico reported on several studies involving a total of 232 patients with liver disorders treated with phytosomal silybin.¹⁸ Daily intakes ranged from 240-360 mg silybin in phytosome form, taken for up to 150 days between meals. Control subjects were also treated with either non-complexed silybin (n=49) or with placebo or no treatment (n=117). Evaluation of efficacy was based primarily on serum liver enzyme levels, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltranspeptidase (GGT). The investigators came to the conclusion that phytosomal silybin had "significant clinical effect."¹⁷ In the population of patients with alcoholic hepatitis, serum AST and ALT returned to normal significantly faster with Siliphos than the reference preparation of non-phytosomal silybin. In another study, patients with acute viral hepatitis (A or B types) fared better on the phytosomal preparation compared to placebo-treated subjects. Similar findings emerged for patients with hepatitis of undetermined cause (so-called iatrogenic cases).

In 1992, researchers at universities in Milan and Bari reported on a controlled study of chronic persistent hepatitis.¹⁹ Patients were randomized to receive either 240 mg silybin phytosome (n=31) or placebo (n=34), one capsule twice daily for three months. The phytosome group experienced significant lowering of both serum ALT and AST, while in the placebo group both enzyme indicators worsened. The silybin treatment was well tolerated, with even fewer adverse events reported than the placebo group, and no patient discontinued the trial due to adverse effects.

A short-term, 1993 pilot study, representing a collaboration between Indena[®] (a manufacturer of a wide range of botanical extracts, including Siliphos) and researchers at the University of Florence, examined the effect of silybin phytosome on 20 patients with chronic active hepatitis (B and/or C).²⁰ During this one-week trial, 10 patients received 480 mg silybin phytosome daily and 10 received placebo. A reduction in serum levels of ALT (29%), AST (25%), and GGT (20%) was observed in the silybin group. Plasma levels of silybin



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were markedly increased at day 7, attaining levels consistent with those measured in the pharmacokinetic studies.¹² In the placebo group, only GGT showed a significant decrease (8% compared to 20% in the silybin group).²⁰ This study also measured serum malondialdehyde (MDA) levels, a byproduct of lipid peroxidation. Although serum MDA fell in the silybin group, it was not statistically significant.

In another very small pilot study, eight patients with chronic active hepatitis (B and/or C) were treated with phytosomal silybin at a daily dose of 240 mg silybin for two months.²¹ Liver enzymes ALT and AST were significantly reduced, while reductions in GGT and MDA did not attain statistical significance. As with the patients in the previous study, baseline MDA levels were very high when the study began. The findings from these two small pilot studies suggest phytosomal silybin is a valuable component of an integrated approach to managing active infection with hepatitis B and/or C viruses. These findings deserve replication in larger and longer studies.

Data particularly useful in establishing dosing recommendations came from a larger 1993 hepatitis trial at the University of Pavia involving 54 patients.²² Patients with chronic hepatitis of either viral or alcoholic origin were randomly assigned to one of three groups. One group (n=19) received phytosomal silybin at 160 mg daily; another group (n=17) received 240 daily; and the third group (n=18) received 360 mg daily. The trial lasted two weeks, with enzyme indicator testing done after weeks 1 and 2. Despite the short duration of the trial, AST was significantly lowered by all dosages. At the two higher doses of 240 and 360 mg daily (but not at 160 mg daily) ALT and GGT were also significantly lowered. Furthermore, at the two higher doses after one week a dose-effect relationship was seen for AST and GGT (although not for ALT) – the higher the dose, the greater the decrease in liver enzymes. In this trial, four of 60 patients experienced adverse effects and two dropped out of the 360-mg group before the end of the first week. The researchers concluded that using phytosomal silybin, an intake of 160 mg silybin daily (one 80-mg capsule twice daily, taken between meals) provided a good maintenance intake. They suggest for better and more reliable results the 240-mg daily intake might be appropriate, and for more difficult cases the 360-mg intake of phytosomal silybin might be indicated.

A small, double-blind trial, published only in abstract form, suggests phytosomal silybin might be useful against hepatitis C in chronically infected patients who do not benefit from interferon treatment.²³ Ten patients who failed to measurably respond to recombinant interferon alpha 2b were studied according to a crossover, randomized, double-blind trial design. After 6-12 months of interferon withdrawal, patients were randomly assigned to receive either phytosomal silybin (360 mg silybin daily) or placebo for two months. After a one-month washout period subjects were crossed over to the other treatment. After statistical analysis phytosomal silybin significantly lowered both ALT and AST, while the placebo failed to do so.

Cirrhosis

Phytosomal silybin is likely safe for cirrhotic patients. Researchers at the University of Padua collaborated with Indena to study uptake of silybin phytosome in 10 patients with compensated liver cirrhosis (Child's Grade A).²⁴ The patients first received a single 120-mg dose of silybin as phytosome daily, and blood silybin levels were monitored. This was followed by a multiple-dose study in which patients received a 120-mg dose twice daily for eight days. The patients absorbed the silybin phytosome as well as healthy subjects, although there was great variability from patient to patient.

In this study, the profile of data from the eight-day dosing period did not show significant differences from the first day's data.²⁴ From this finding the researchers concluded that (on average) patients were not accumulating silybin in poorly functioning livers, nor were any clinically adverse effects reported. Another study on cirrhotic patients (n=9) used a higher dose of silybin as phytosome (360 mg) for one day.²⁵ Great inter-patient variability was found, with no clinically adverse effects. Since hepatitis patients can develop adverse effects at this high intake,²² such short-term experience does not prove this dosage is safe for long-term use by patients with cirrhosis.

Side Effects and Toxicity

This phytosomal form of silybin has been studied for safety.^{4,18,26} Overall, it is well tolerated in humans. According to researchers Marena and Lampertico,¹⁸ healthy volunteers (total number not disclosed) received 360 mg silybin-phytosome complex three times

daily for three weeks without adverse effect. They also reported treating 232 patients with “liver disorders” for up to four months with either 240 or 360 mg daily, concluding the tolerability of the silybin-PC preparation was excellent. Minor adverse effects (nausea, heartburn, dyspepsia, transient headache) were reported in 12 patients (5.2% of the total studied), compared with 8.2 percent of patients who received non-complexed silybin and 5.1 percent of patients on placebo. In other words, adverse effects of phytosomal silybin were essentially the same as placebo. The phytosomal silybin produced no clinically relevant blood changes in these patients.

Phytosomal silybin has also proven safe in traditional toxicological tests. Oral acute toxicity is >5,000 mg/kg body weight in rats, dogs, and monkeys. After 13-week subacute toxicity studies the preparation was found safe for rats and monkeys at oral doses up to 2,000 mg/kg body weight/day. In 26-week chronic toxicity studies, oral doses up to 1,000 mg/kg body weight/day were well tolerated in rats and dogs. In another 26-week oral toxicity study, rats were fed a daily 2,000 mg/kg body weight dose of Siliphos, equivalent to 160 g daily for a 176-pound (80 kg) human. As published by Indena, body weight, liver weight, and enzyme indicators of liver damage (AST, ALT) remained within the normal, healthy range of the untreated control rats.²⁷ Pharmacological studies in mice, rats, and dogs indicate phytosomal silybin does not adversely affect central nervous system, cardiovascular, or respiratory functions, and does not influence stomach emptying or intestinal motility, at oral doses as high as 1,000 mg/kg body weight. The silybin-PC complex had no evident adverse effects on reproduction in rats and showed no mutagenic effects in several test systems.²⁶

Silymarin and silybin are well tolerated. Silybin intakes up to 1,080 mg/day as phytosome are well tolerated even by patients with compensated cirrhosis.²⁸ A 2007 trial that utilized the silybin phytosome for prostate cancer determined that up to 13,000 mg/day of the phytosome (providing about 3,900 mg/day of silybin) is well tolerated by patients with advanced cancer.²⁹

Dosage

While silymarin (typical standardized milk thistle extract) must be taken at doses of approximately 420 mg daily to achieve benefit, silybin (complexed with phosphatidylcholine) can produce benefit at intakes as

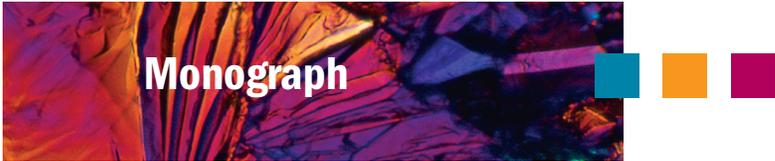
low as 120 mg (400 mg silybin-PC complex) daily, and can be safely administered regularly at doses of 240-360 mg (800-1,200 mg silybin-PC complex) daily.

Acknowledgement

For more extensive reviews of silybin-phosphatidylcholine complex and phytosome complexes in general, see Kidd’s reviews in *Altern Med Rev*, volumes 10(3) and 14(3), excerpts of which appear in this monograph.

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Life Extension Magazine May 2010

REPORT

The Overlooked Compound That Saves Lives

By Julius Goepf, MD

N-ACETYL CYSTEINE

For more than three decades, a safe, low-cost compound has provided millions of people relief from the coughing, wheezing, and thick phlegm associated with cold and flu. Of course, pharmaceutical companies long ago co-opted it for profit by incorporating it into various patented drugs.



The sad consequence is that most aging individuals have never heard of it. Even many doctors remain unaware of its potential role as a frontline defense against some of today's most deadly public health threats, including:

- **Acetaminophen toxicity and acute liver failure:** the number one cause of acute liver failure in the United States.¹
- **Influenza:** whose victims are primarily aging individuals—**three quarters** of all flu-related deaths occur in the elderly.²
- **Chronic obstructive pulmonary disease:** the fourth-leading cause of death in the United States (includes **emphysema** and **chronic bronchitis**).²
- **Helicobacter pylori:** the bacterial culprit behind stomach ulcers, and a potentially lethal pathogen closely linked to malignant gastric cancer, the second most *frequent* cause of cancer death worldwide.³

Fortunately, renewed clinical interest in its broad-spectrum benefits is yielding fresh data on promising interventions for this safe, effective compound.

In this article, you will discover the latest research on **N-acetyl cysteine** (NAC), a readily available, inexpensive amino-acid derivative with four decades of scientific validation. You will learn of its role in restoring intracellular levels of one of the body's most powerful antioxidant defenses, **glutathione** (GSH). You will also find out how **600-1,800 mg** of NAC daily may act as an effective intervention against a constellation of chronic, degenerative diseases, including impaired glucose control and cancer.

AN UNDERUTILIZED INTERVENTION

NAC is a slightly modified version of the sulfur-containing amino acid cysteine. When taken internally, NAC replenishes intracellular levels of the natural antioxidant glutathione (GSH), helping to restore cells' ability to fight damage from reactive oxygen species (ROS).

NAC has been used in conventional medicine for more than 30 years, primarily as a mucolytic (mucous-thinner) inhaled to manage conditions such as cystic fibrosis, in which mucous is abnormally thick and tenacious. While there is little in the scientific literature to support its use as an inhalant, NAC administered in this form remains highly popular among experienced pulmonary specialists.^{4,5}

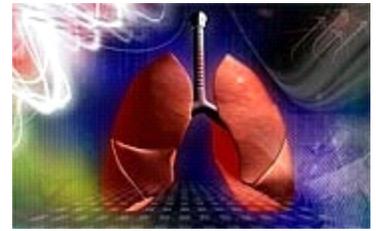
NAC given intravenously or orally, on the other hand, saves lives every year as a treatment for acute poisoning with acetaminophen-containing pain-relieving drugs. Acetaminophen is sold as Tylenol® and combined with other drugs to create analgesic compounds, including Vicodin® and Percocet®.⁶ Overdoses with acetaminophen are the number one cause of acute liver failure in the United States.⁶⁻⁸ Too much acetaminophen overwhelms the body's glutathione reserves, which creates widespread and irreversible liver damage. NAC quickly restores protective levels of glutathione, averting catastrophe.⁷

Beyond this particular application, NAC has remained a relatively obscure and poorly understood compound until quite recently. Scientists all over the world are now beginning to understand just how vital glutathione metabolism really is, and how many

disease states involve glutathione deficiency.⁹ According to Stanford University's Dr. Kondala R. Atkuri, "NAC has been used successfully to treat glutathione deficiency in a wide range of infections, genetic defects and metabolic disorders, including HIV infection and COPD. Over two-thirds of 46 placebo-controlled clinical trials with orally administered NAC have indicated beneficial effects of NAC measured either as trial endpoints or as general measures of improvement in quality of life and well-being of the patients."⁹

MULTITARGETED REGULATION OF GENE EXPRESSION

Much of NAC's beneficial activity derives from its capacity to modulate expression of genes for myriad signaling molecules in the inflammatory response.¹⁰⁻¹² NAC inhibits expression of pro-inflammatory cytokines following exposure to bacterial cell components and infection with influenza A virus.^{13,14} NAC suppresses the "master signaling molecule" nuclear factor-kappaB (NF- κ B), which in turn prevents activation of multiple inflammatory mediators.^{15,16} NAC also regulates the gene for COX-2, the enzyme that produces pain- and inflammation-inducing prostaglandins in a wide array of chronic conditions.¹⁷



NAC's ability to replenish the intracellular glutathione supply and mitigate oxidative damage is a separate and equally powerful mechanism that affords protection against DNA damage and cancer development, even in smokers.¹⁸ NAC's inhibition of inflammatory cytokine production is another mechanism credited with cancer reduction in various body tissues.¹⁹

Gene expression modifications induced by NAC may also help reduce the acute oxidant-provoked inflammatory response following exercise, making vigorous activity safer and even more beneficial.²⁰ Finally, obesity-associated insulin resistance, which arises from production of inflammatory signaling molecules in fat cells, can be sharply mitigated by NAC through regulation of their genes.^{21,22}

The recent explosion of scientific evidence for NAC's multi-targeted health benefits is matched only by the willful ignorance of the mainstream medical community. Some even question its safety, despite nearly 40 years of use in a variety of clinical conditions, which have established the safety of this compound, even at very high doses and for long-term treatments.¹⁸ One study demonstrated the safety of 1,800 mg per day for 142 days, while another study demonstrated the safety of 2,800 mg per day for 3 months.²³

Here is a selection of the most compelling information about NAC from the global scientific community—information that should convince even skeptical mainstream physicians.

WHAT YOU NEED TO KNOW: N-ACETYL CYSTEINE'S BROAD-SPECTRUM BENEFITS

- Long relegated to infrequent use in unusual circumstances, the amino acid-derived compound N-acetyl cysteine (NAC) has drawn increased scientific attention.
- NAC replenishes levels of the intracellular antioxidant glutathione (GSH), which is often deficient with advancing age and in chronic illness.
- NAC also regulates expression of scores of genes in the pathways that link oxidative stress to inflammation.
- These dual effects give NAC a unique role in the prevention and treatment of many common diseases, both acute and chronic.
- NAC can protect against avian influenza and more common seasonal flu symptoms.
- NAC reduces the frequency and duration of attacks of chronic obstructive pulmonary disease (COPD) and may slow the clinical course of idiopathic pulmonary fibrosis (IPF).
- NAC protects tissues from the effects of exercise-induced oxidative stress, adding value and safety to your workout.
- NAC improves insulin sensitivity in people with some of the most difficult-to-treat metabolic disorders.
- NAC blocks cancer development at virtually every step in the process, and through multiple mechanisms, making it an important cancer chemopreventive agent.
- NAC fights the stomach infection *Helicobacter pylori* on two fronts, inhibiting the organism's growth while reducing production of inflammatory cytokines that can lead to gastritis and cancer.
- Though most individuals gain benefits from 600-1,800 mg/day, clinical studies have found that doses of up to 2,000 mg/day are safe and effective. A recent study demonstrated the safety of 2,800 mg/day for 3 months in patients with COPD.²³

POTENT INFLUENZA PROTECTION

H5N1 influenza, or bird flu, is a lethal and potentially pandemic infection that produces the massive release of inflammatory mediators aptly called the “cytokine storm.”²⁴ Other more common forms of influenza also act by triggering massive cytokine releases that inflame vulnerable lung tissue. In early 2010, it was discovered that NAC offers dual protection against bird flu. It inhibits both virus replication and expression of pro-inflammatory molecules in cells infected with H5N1 virus, holding out the promise of effective protection in the event of a global avian flu pandemic.¹³

NAC has also proven effective against seasonal influenza and flu-like illnesses. In a large study of older adults who took 600 mg twice daily for 6 months, only 25% of those experienced influenza-like episodes, compared with 79% in the placebo group.²⁵ Even those with flu symptoms experienced a significant reduction in illness severity and length of time confined to bed. All subjects tolerated the treatment well. The study’s lead author, Dr. Silvio de Flora, commented that “Administration of N-acetyl cysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk individuals.”²⁵



Influenza is a complex disease with multiple targets, most notably inflicting damage to lung tissue through extreme oxidative stress and inducing genes for a large variety of inflammatory mediators.^{26,27} At the microscopic level the destruction is vivid. The influenza virus causes such intracellular turmoil that the term “cell boiling” has been used to describe the devastation.²⁸ But pretreatment of cells with NAC significantly offsets these effects, reducing the oxidative and inflammatory burden within lung tissue through multiple mechanisms.^{26,28-30}

NAC has now been shown to protect laboratory mice from lethal influenza infection, synergistically enhancing the effects of several common antiviral medications.^{31,32} And a nutrient mixture containing NAC, green tea extract, certain amino acids and micronutrients had powerful antiviral effects in cultured cells, rivaling those of prescription flu drugs such as amantadine and oseltamivir (Tamiflu®).^{33,34} The NAC-based mixture actually affected viral replication for a longer period than did the drugs.³⁴

In the words of prolific medical theorist Mark F. McCarty, “The most foolproof way to promote survival in epidemics of potentially lethal influenza is to target... intracellular signaling pathways which promote viral propagation or lung inflammation.”³⁰ McCarty goes on to cite NAC’s benefits as a multitargeted supplement with precisely those attributes. NAC at doses of 600 mg twice daily may significantly reduce the risk of a devastating bout of influenza.

NAC AND PULMONARY ARTERIAL HYPERTENSION: A REAL RISK?

N-acetyl cysteine (NAC) produces numerous beneficial effects in many human tissues both by supporting natural antioxidant systems and by favorably affecting expression of genes involved in the inflammatory response.

A 2007 study in laboratory mice, however, has raised a theoretical concern that chronic NAC administration in those animals might produce a condition called pulmonary arterial hypertension.⁷⁶ Here is a review of that study and some reassuring facts:

THE ISSUE

Pulmonary arterial hypertension (PAH) is an elevation in blood pressure in the arteries leading from the heart to the lungs. It is one of the consequences of *chronic hypoxia* (lack of sufficient oxygen) that occurs in a number of chronic cardiovascular and pulmonary (lung) diseases. It also arises in people with obstructive sleep apnea.⁷⁷⁻⁷⁹ It is a rare condition, but when it occurs it can be difficult to detect and may be fatal if untreated.⁷⁹ Its causes remain unclear, but they seem to involve signaling molecules produced during hypoxia; some of those molecules include those involved in detecting and responding to oxidative stress.⁸⁰

THE CONCERN

Scientists at the University of Virginia School of Medicine were studying the molecular signaling involved in hypoxia-related development of PAH when they observed what seemed to be a concerning finding: mice treated with NAC over periods of 3 weeks were developing PAH that mimicked the effects of chronic hypoxia.⁷⁶ The scientists were not studying the effects of NAC itself; they were simply using it to measure other nitrogen-related transfer reactions in blood. And the doses they used correspond to a human dose of about **20 grams** (20,000 mg) per day—far above any known supplement recommendation. Nevertheless, parts of their report were cited in one commentary as raising “the concern that chronic NAC therapy may induce similar vascular pathology in patients.”⁸¹

Is this a realistic concern, or is it a laboratory anomaly? Here’s the evidence to date.

THE EVIDENCE

The Virginia team's mouse study was published in 2007. Now, nearly 3 years later, there has not been a single additional publication connecting NAC therapy with PAH in either animals or humans. In reality, a substantial amount of science both before and after the 2007 report suggests just the opposite—that NAC may be instrumental in reducing, not increasing, the oxidant-induced blood vessel changes that occur in PAH. Here are the highlights:

- In one of the original animal studies demonstrating that oxidative stress contributes to development of PAH induced by hypoxia, NAC actually reduced the heart and lung changes that lead to PAH, in part by reducing toxic peroxide molecules.⁸⁰
- NAC, given before and at the beginning of experimental hypoxia, was effective at preventing PAH, including deadly heart muscle changes, in laboratory rats.⁸²
- NAC protects experimental animals' lungs from the acute lung injury caused by a variety of mechanisms involving hypoxia, oxidant stress, and inflammation, through its joint antioxidant and anti-inflammatory actions.^{83,84}
- A study of human volunteers revealed that NAC supplements at **1,800 mg/day** *increased* the healthy respiratory response to hypoxia,⁸⁵ which normally declines strongly with age and may contribute to PAH.⁸⁶ Although this study was cited by the Virginia group as supporting their concern about NAC inducing PAH, no such evidence is presented in the human study, and in fact the authors conclude that NAC treatment "may be useful for elderly subjects and for patients who have other conditions with an oxidative shift... such as coronary heart disease and malignant diseases."⁸⁵

THE RECOMMENDATION

There have been no further publications supporting this one-time observation made in an animal model using doses 10-20 times those suggested for long-term human supplementation. No human study has uncovered any evidence for a similar effect in humans. By contrast, there have been numerous studies demonstrating human benefit from NAC supplementation at moderate doses (1,200-1,800 mg per day) over the course of nearly 4 decades. At this point the known benefits of NAC appear to outweigh any potential risks. As with all supplementation, people should communicate clearly with their healthcare providers about how supplements and medications might work jointly to influence their health.

Life Extension Magazine May 2010

REPORT

The Overlooked Compound That Saves Lives

By Julius Goepp, MD

LUNG DISEASE DEFENSE

Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and chronic emphysema, is a rapidly growing problem with global impact.³⁵ COPD is the result of years of oxidative damage to delicate lung tissue, with resultant chronic inflammatory changes.³⁶ The disease is worsened by air pollution and cigarette smoking, but is by no means limited to people with those exposures. Over time, victims' damaged airways may become colonized with dangerous bacteria, leading to chronic infection and still more inflammation in a vicious cycle. Current treatment consists mainly of anti-inflammatory steroids and lung-opening medications used in asthma, with the addition of antibiotics when infection threatens.



With its ability to reduce oxidative stress and simultaneously quash chronic inflammatory changes, NAC is emerging as a game-changing therapy in COPD. A randomized pilot study of adults with acute exacerbation of chronic bronchitis and positive bacterial culture in the sputum demonstrated that 600 mg of NAC twice daily led to a near doubling of the rate of bacterial eradication compared with standard therapy, while reducing the number and duration of acute exacerbations and improving quality of life.³⁵ NAC treatment of patients with moderate-to-severe COPD improved their physical performance on lung function tests, especially after exercise.³⁷

Patients with advanced COPD frequently require low-dose oxygen therapy because of their lung damage. In many cases, however, oxidative stress induced by the disease has already rendered them glutathione deficient, so they have diminished protection against ongoing oxidation.³⁸ NAC administration at doses of 1,200-1,800 mg/day along with low-dose oxygen powerfully counteracts this oxidative stress. At doses of 1,800 mg per day, it has been shown to completely prevent further protein oxidation.³⁸ A dose of 600 mg twice daily over a 2-month period rapidly reduced exhaled hydrogen peroxide, a measure of oxidative burden in COPD sufferers.³⁹

In one study utilizing a dose of just 600 mg per day for 10 weeks, NAC disrupted the molecular relationship between oxidative stress and inflammation, protecting lung tissue.³⁶ When NAC is added to inhaled corticosteroids, still further reductions in inflammatory parameters are found.⁴⁰

Emphysema can be the unfortunate endpoint of advanced COPD, with lung tissue breaking down and losing much of its ability to exchange oxygen and carbon dioxide. Animal studies show that NAC attenuates COPD-related lung damage and emphysema by supporting expression of important protective genes in the cells lining the lung.⁴¹

Another devastating chronic lung condition called idiopathic pulmonary fibrosis (IPF) also involves increased oxidative burden and a deficiency of glutathione in lung tissue and fluids.⁴² This progressive disease has a poor prognosis, even when treated with standard corticosteroids and powerful prescription anti-inflammatory drugs.^{43,44} The median survival is only about 3 years regardless of therapy.⁴⁵

Oral NAC supplements now offer a ray of hope for IPF sufferers. NAC significantly increases lung glutathione levels in both animal and human studies of IPF.^{42,46} Given as an aerosol treatment, NAC may delay disease progression, and at doses of 600 mg three times daily preserves lung vital capacity and gas exchange better than standard therapy alone.^{43,44}

In summary, evidence suggests that NAC may offer benefits at doses of 600 mg 2-3 times daily for people who have, or are at risk for, chronic lung conditions such as COPD and IPF (idiopathic pulmonary fibrosis).

REDUCE EXERCISE-INDUCED OXIDATIVE STRESS

Health-conscious people know that regular moderate exercise is vital to maintaining the integrity of the human body. Of course, everything has its price, and the rapid increase in metabolic activity during exercise produces some unwanted side effects.²⁰ These include an increase in oxidative stress that can overwhelm the body's antioxidant defense mechanisms and lead to tissue damage and abnormal activity of certain immune system cells.^{47,48} Exercise also increases plasma levels of inflammatory cytokines such as TNF-alpha and various interleukins.⁴⁹ The solution, of course, is not to reduce your exercise regimen, but rather to look for ways to optimize the way your body handles those metabolic challenges.

NAC, with its powerful antioxidant and gene-regulating powers, is an excellent means of maintaining good exercise performance and limiting the damage caused by oxidative stress in the process. Supplementation with NAC (2,000 mg daily for 3 days, followed by 800 mg prior to exercise) in strenuously exercising adults lowered key interleukin levels to undetectable amounts and abolished the exercise-induced TNF-alpha response.⁴⁹ And in patients with severe COPD, NAC supplementation improved exercise endurance time by 25% compared with placebo, while significantly reducing levels of oxidative molecules released by stimulated immune cells.⁵⁰ NAC supplementation also dramatically curtailed production of oxidized proteins in this group of highly oxidant-stressed chronically ill patients.



In vigorously exercising men, 1,800 mg per day of NAC prevented the expected decline in intracellular antioxidant levels and increased activity of the enzyme responsible for recycling and restoring glutathione to normal levels, protecting cells from oxidative stress.⁵¹ And in mice, NAC supplementation significantly protected brain tissue against exercise-induced oxidative changes.⁵² NAC also preserves normal levels of vital lymphocytes, which can decline after vigorous exercise.^{48,53-55}

Regular supplementation with NAC at up to 1,800-2,000 mg per day may be an effective means of optimizing exercise performance while minimizing the effects of exercise-induced metabolic stress.

BRING GLUCOSE LEVELS UNDER CONTROL

Oxidative stress and inflammation are closely linked to insulin resistance and rising blood glucose levels. These effects are not limited to those with diabetes, but in fact are found even in obese, non-diabetic people and those with metabolic syndrome.⁵⁶ There are multiple steps in the cascade of events leading from oxidation to damaged insulin receptors and insulin resistance, so it makes sense to seek a supplement that can target many of those steps independently.^{57,58} NAC is emerging as one such

multi-targeted supplement.⁵⁶

Over time, chronic high blood sugar initiates a downward spiral by helping generate advanced glycation end-products (AGEs) that then impair normal responses to insulin, perpetuating elevated sugar levels. NAC reverses those effects in laboratory models.²² Increasing blood sugar levels in laboratory animals triggers a pro-inflammatory response in fat tissue—also effectively reduced by NAC.²¹ In an experiment that recreates a common human dietary trend, rats were given a diet high in the sweetener fructose, which produced increased blood pressure, plasma insulin levels, and triglyceride levels. Yet all of these dangerous physiological alterations were inhibited by NAC.⁵⁹

Human studies of NAC to improve insulin sensitivity have recently appeared, especially in a group of people typically very difficult to treat. Profound insulin resistance is seen in women with polycystic ovary syndrome (PCOS), along with a variety of other metabolic disturbances. One study showed that NAC at 1,200 mg per day along with 1,600 mg of the amino acid arginine promoted a trend toward normal ovulatory cycles and substantially improved insulin sensitivity.⁶⁰ A short-term study showed that 1,800 mg of NAC daily helped improve insulin sensitivity in women with PCOS.⁶¹

Virtually all Americans consume too many calories and are at risk for at least some degree of insulin resistance. Daily supplementation with NAC at 1,200 to 1,800 mg per day may help to reduce the impact and slow the damage wrought by AGEs.

CANCER PREVENTION

The strong and growing links between oxidative stress, inflammation, and cancer make NAC a natural go-to compound for cancer chemoprevention. True to form, NAC has multiple anti-cancer activities acting at multiple targets to provide layers of cancer protection against a large variety of cancer types. NAC induces programmed cell death (apoptosis) in multiple types of human cancer cells.⁶² In human gastric cancer cells, NAC not only induces apoptosis, but also stops DNA synthesis, preventing cancer the cells from replicating.⁶³ In melanoma cells, NAC inhibits NF-κB, preventing expression of signaling molecules needed by the cancer for growth.⁶⁴ NAC inactivates and promotes destruction of c-Src, a chemical control molecule that is overproduced in many human cancers, providing a completely unique means of slowing or stopping tumor development.⁶⁵ Finally, NAC protects DNA from breakage induced by ionizing radiation, but does not prevent cell destruction by radiation.⁶⁶ That's a vital finding because it means that NAC might allow radiation therapy to effectively kill cancer cells while minimizing the risk of so-called secondary cancers that could otherwise arise as side effects of the radiation.

Animal studies strengthen the case for NAC still further. NAC protects mice from cigarette smoke-induced lung cancers and other lung changes, a finding with enormous implications not only for current smokers but for ex-smokers and people exposed to second-hand smoke.⁶⁷ NAC protects rats from chemically-induced liver cancers immediately following tumor initiation.⁶⁸ This early interference with cancer development bodes well for NAC as a chemopreventive agent in the many human toxin-related cancers.

Human studies are similarly encouraging, even in the most challenging patient groups such as smokers. A randomized, double-blind chemoprevention trial of NAC 600 mg twice daily for 6 months vs. placebo in otherwise healthy smokers showed a significant reduction in formation of damaged or oxidized DNA segments, telltale early markers of cancer development in lung fluid.⁶⁹ The same study also demonstrated reductions in abnormal, pre-cancerous cell changes in the mouths of supplemented smokers. These effects support the scientists' conclusion that NAC can reduce tobacco smoke carcinogenicity in humans.

Colon cancer is another malignancy with strong links to oxidative stress and inflammation. Preliminary studies in humans show a 40% reduction in colorectal polyps in patients given 600 mg per day of NAC, compared with controls.⁷⁰ In a group of people with a previous history of pre-cancerous colonic polyps, 800 mg per day of NAC for 12 weeks significantly reduced the proliferative index, indicating a decreased risk of colon cancer.⁷¹

Supplementing with 600-1,200 mg per day of NAC appears to be an entirely appropriate means of adding to your general cancer-prevention strategy.

GASTRITIS, ULCERS, CANCER, AND HELICOBACTER PYLORI

Helicobacter pylori is a bacterium that colonizes various regions of the stomach and upper part of the small intestine. *H. pylori* infection produces major oxidative stress on tissues already vulnerable to extremes of pH and other chemical challenges, and the resulting inflammation produces pain and promotes development of gastric and esophageal cancers.¹⁹ NAC is an obvious candidate for fighting *H. pylori* infections, both because of its powerful ability to interfere with the oxidant-inflammation connection, and also because of its potential to break down some of the gastric mucous layer beneath which the organism hides.⁷²

NAC fights *H. pylori* in at least two ways. It markedly inhibits growth of *H. pylori* both in culture dishes and in live mice, helping to

reduce the total load of organisms present.⁷² But NAC also powerfully regulates gene expression in stomach lining cells, reducing hydrogen peroxide production induced by *H. pylori*, and decreasing activation of NF- κ B and subsequent release of inflammatory cytokines.^{19,73} In human trials NAC improves eradication rates of *H. pylori* produced by standard treatment with antacids and antibiotics, when given at doses of **1,200 mg** per day.^{74,75}

People who have gastritis or gastroesophageal reflux disease (GERD) may be infected with *H. pylori* and may benefit from supplementation with **1,200 mg** per day of NAC, especially during co-treatment with drugs to eradicate the organism.

SUMMARY

N-acetyl cysteine is a broad-spectrum compound traditionally under-utilized in conventional medicine. A burst of new clinical research reveals that NAC exerts dual effects, functioning both as a powerful antioxidant that replenishes cellular antioxidant systems (glutathione in particular) and also as a potent modulator of gene expression, regulating inflammation at multiple, fundamental levels. It has been shown to be an effective intervention against influenza, chronic lung diseases, cancers, insulin resistance, and gastritis caused by *H. pylori*. NAC's further value is shown in its ability to mitigate otherwise inevitable metabolic and immunological disturbances caused by exercise.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

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