PSYCHIATRY REDEFINED

Continuing Education in Functional and Integrative Psychiatry

# *Preventing Cognitive Decline and Dementia*

JAMES GREENBLATT, MD

# TABLE OF CONTENTS


**Introduction: Preventing Cognitive Decline and Dementia ..... 4**
Cognitive Decline Protocol

**The Burden of Alzheimer's Disease ..... 5**

**The Promise of Natural Lithium for the Prevention of Dementia ..... 7**
Lithium: A Brief History
Lithium for Cognitive Decline: Early Evidence
The Promise of Low-Dose Lithium
But How Does It Work? Key Neuroprotective Mechanisms
Lithium: Keystone of a Multifactorial Approach to Alzheimer's Treatment and Prevention

**A Multifactorial Approach: B-Vitamins, and Homocysteine Testing for Prevention ..... 11**
The B Vitamins (Vitamin B12, Folate and Vitamin B6) and Homocysteine
*Homocysteine*
*Mitigating the Risk of Cognitive Decline with B-Vitamins: Evidence*

**Fortifying the Nutritional Armor: Compounds Conferring Additional Protection ..... 15**
Curcumin
*Curcumin for Cognitive Decline: Biologic Mechanisms & Research Evidence*
*Curcumin for Cognitive Decline: Challenges in Application*
*Theracurmin®*
*Meriva®*
N-Acetylcysteine (NAC)
Polyphenols
*Grape Polyphenols*
*Blueberry Polyphenols*
*Pine Bark Extract*
*Green Tea Extract*
Omega-3 Fatty Acids
*Omega-3s: A Review*
*Omega-3 Deficiency: Implications for Health*
*Omega-3s and Cognitive Decline*
*Omega-3 Supplementation*

**Treatment Protocol ..... 24**
Supplementation
*Luma TC*
*CurcumaSorb Mind*

**Summary ..... 26**
Opening the Therapeutic Toolbox: Answers to Alzheimer's & Cognitive Decline

**Appendix ..... 27**
Alzheimer's Risk Factors Suggesting the Need for Prevention

## In the time it has taken you to open this book, someone somewhere has developed dementia.

This is neither conjecture nor an exaggeration. Current statistics indicate that there is a new dementia case somewhere in the world every three seconds, a new drop in a rising ocean of medical need for which modern medicine has no viable answer (ADI 2021).

Approximately 50 million people on the planet currently live with some form of dementia, the most common form of which is Alzheimer's disease (WHO 2020). Epidemiologic data reveal dementia and Alzheimer's incidence rates to be on a meteoric rise, and there is no indication that rising rates will start slowing anytime soon. Projections from the World Health Organization (WHO) forecast the total number of cases worldwide to rise to 152 million by 2050 (WHO 2020). Overall, numerous risk factors have been associated with developing dementia, including increasing age, diabetes, and heart disease among others (see appendix for a more complete list).

### Cognitive Decline Protocol

In 2018 I authored *Integrative Medicine for Alzheimer's* (Greenblatt 2018). This book outlines an evidence-based approach to the prevention and treatment of dementia, the foundation of which is the clinical use of micronutrients (such as low-dose lithium and other essential vitamins and minerals) to address the underlying risk factors.

I felt that it was of paramount importance to spread the word regarding strategies for the prevention of Alzheimer's and cognitive decline—strategies supported by overwhelming empirical evidence yet widely and persistently ignored by the mainstream healthcare establishment.

The dogged adherence by mainstream medicine to a reactionary, medication-based approach to Alzheimer's treatment—an approach that has *never*, as of the date of this writing, been shown to be effective—becomes unacceptable when science itself has proven that there is another way. Again, we have only to adjust our thinking, becoming proactive instead of reactive, to see that there is hope for Alzheimer's. Already-available research, much of it from the very healthcare establishment that so vehemently refuses to alter its own ineffective models, shows us how we can translate this evidence into hope for a better future.

Inspired by the knowledge that *we can do better*, as well as overwhelming concerns regarding the continued escalation of the Alzheimer's disease epidemic, I wanted to summarize my approach with updated references and a succinct, straightforward, easy-to-implement treatment plan.

*Preventing Cognitive Decline and Dementia* lays out an effective approach for the treatment and prevention of Alzheimer's dementia and other forms of cognitive decline that is based upon key tenets of Functional Medicine. As such, it prioritizes several lab tests that provide a snapshot of patients' unique needs.

*The dogged adherence by mainstream medicine to a reactionary, medication-based approach to Alzheimer's treatment—an approach that has never, as of the date of this writing, been shown to be effective—becomes unacceptable when science itself has proven that there is another way.*

Specifically, individuals should be evaluated for deficiencies or imbalances of critical nutrients via two key laboratory tests:

- Vitamin B12 (serum B12)
- Homocysteine

Based on the results of this testing, a targeted regimen of nutritional supplementation to correct imbalances or deficiencies should be implemented.

Next, the administration of nutritional supplements with scientifically-researched ingredients should be considered for treatment and prevention:

- Luma TC (contains lithium, N-acetylcysteine, folate, B12, B6, and TC [sub-micron particle curcumin])
- CurcumaSorb Mind (contains curcumin and extracts of grape, blueberry, pine bark and green tea)
- Fish oil

The rationale for this approach, and the use of these specific nutrients and supplements will be explained in this book. Readers will learn how these compounds can affect cognitive decline and dementia, and explore published research that supports their efficacy and clinical utility. Finally, this book will present a full protocol for the use of these supplements as part of a Functional Medicine approach for Alzheimer's and cognitive decline.

## CHAPTER 1

# *The Burden of Alzheimer's Disease*

Cognitive decline (CD; a precursor to dementia) and dementia are devastating—devastating for those who suffer from them, and often devastating for patients' friends and family members. Initial symptom onset is often subtle. Yet the condition inexorably progresses, a slow tipping of the neurologic scales away from health and towards disease.

People in early symptomatic stages of CD or Alzheimer's often function independently, and may maintain a normal level of engagement in everyday activities. However, they may start to notice that they are suffering from intermittent memory lapses - perhaps trouble remembering familiar words or the location of familiar objects - and that they become confused more easily than they used to. The awareness of impaired memory can be extraordinarily frightening. People with early-stage cognitive decline may become depressed in response to the increased challenges associated with navigating everyday life...particularly when tasks and activities that used to be easy slowly become more difficult (AA 2021).

This is just the beginning of symptomatic Alzheimer's disease and—invariably—things only get worse.

In later, more severe stages of the disease, people with Alzheimer's may appear as shells of their former selves, no longer able to recognize friends or family or complete simple tasks requiring even minimal memory processing. Difficulty with controlling bladder and bowels, changes in sleep patterns, difficulty communicating, delusions, compulsive and repetitive behaviors...these are just a few of the symptoms of late-stage (severe) Alzheimer's and dementia, at which point the sufferer typically requires 'round-the-clock assistance and personal care (AA 2021).

People with Alzheimer's typically live four to eight years beyond clinical diagnosis, during which time expenses associated with their required care can accrue to staggering levels. (AA 2021). As of 2020, total healthcare costs for Alzheimer's disease care are estimated at $305 billion dollars, with costs expected to increase to $1 trillion by 2050 (Wong 2020).

Stunning as they are, these figures pale in comparison with the "other" costs of Alzheimer's. The emotional and psychological tolls exacted by Alzheimer's, borne by victims' friends, family members, and loved ones, are incalculable.

As it stands, a diagnosis of Alzheimer's is a de facto death sentence, for there is no standard treatment that can slow or reverse the disease to any significant degree (Isla 2021). In a very macabre way, there is a great deal of certainty associated with Alzheimer's disease; patients *will* deteriorate, progressively and continuously, and *will* eventually die from the disease. As such, Alzheimer's disease is currently the seventh leading cause of death in the United States, only falling one place in the last year due to the COVID-19 pandemic (Ahmad 2021).

But does it have to be this way?

On the pharmaceutical front, it appears so, at least as of the time of this writing. Efforts towards developing effective drug treatments have failed repeatedly. From 2002 to 2012, 99.6% of all drug trials for Alzheimer's disease were unsuccessful. And those trends have only continued (Cummings 2018).

Dark though this backdrop may be, there are two significant glimmers of hope that have lately emerged against it. The first of these is the discovery that Alzheimer's and other forms of progressive neurodegenerative decline typically take years to fully develop.

Studies have confirmed that the biologic processes underlying cognitive decline may commence decades before symptoms begin to manifest (Vermunt 2019). It's during this time—particularly in the early stages—that the evidence suggests that Alzheimer's may be most treatable and is *not* necessarily a foregone conclusion (Aisen 2015).

The potential significance of these revelations simply cannot be overstated. Since Alzheimer's disease has a long initial period of disease progression without symptoms, targeting risk factors early may revise or halt this progression.

The second glimmer of hope emerging on the horizon goes hand-in-hand with the first: natural products that have largely been hidden behind the hype of pharmaceutical trials, and ignored by the press, have shown some significant potential. While Big Pharma funnels billions into initiatives to discover "magic bullet" cures, these humble nutraceuticals are stepping ever further into the limelight as research has continued to confirm their efficacy in preventing and possibly treating dementia and cognitive decline.

Among the natural products demonstrating such tremendous promise, the mineral lithium is a notable standout.

> *Known to western medicine for years for its mood-stabilizing and cognition-enhancing properties, and a gold-standard intervention in the therapeutic arsenal for bipolar disorder even today, lithium has made ripples as a preventative and potential treatment for dementia. And these are substantial ripples too; a 2011 trial went so far as to tout lithium as the first potential disease-modifying agent in the treatment of Alzheimer's (Forlenza 2011).*

In this book we will explore research on the efficacy, safety, and utility of low-dose lithium for the treatment and prevention of dementia. In line with a multifactorial treatment approach, we will also explore powerful evidence supporting the utility of other natural substances as well as risk factors for dementia; notably, deficiencies in the B-vitamins, and elevations of the brain-toxic compound, homocysteine.

The success of this paradigm hinges, ultimately, on our willingness to adopt a different perspective, flipping the telescope through which we have observed the Alzheimer's phenomenon.

**Instead of viewing Alzheimer's, dementia, and other forms of cognitive decline through a lens of inevitability, we can accept that Alzheimer's susceptibility lies along a continuum of risk which is dynamic...and thus alterable. Instead of taking reactionary steps to an already-established case, we can focus our efforts on prevention. Instead of focusing on one singular disease pathway, we can use safe natural substances with proven protective properties to foster brain health through a variety of pathways, implementing a comprehensive, balanced, and multifactorial approach for the fortification and preservation of the human mind.**

CHAPTER 2

# *The Promise of Natural Lithium for the Prevention of Dementia*

The mineral lithium has shown tremendous promise for the treatment and prevention of Alzheimer's disease and other forms of cognitive decline. This humble element has an extensive history of medicinal use, founded in its long-established benefits for a range of emotional and cognitive ailments.

## Lithium: A Brief History

By the time lithium was first isolated as a mineral salt by Swedish chemist Johan August Arfvedison in 1817, its use in traditional pharmacological preparations already spanned millennia. The first documented use of lithium was in the 2nd century AD by Seranus Ephesios, A Greek physician who prescribed bathing in alkaline springs, likely containing high levels of lithium, for the treatment of mania (Georgotas 1981). These lithium-rich mineral springs, and others like them throughout the world, remain sought-after health destinations, frequented throughout the ages by rulers and commoners alike.

Throughout the 19th and early 20th centuries, lithium was used as a supplement to fortify a variety of foods and beverages. The third edition of *The Merck Index*, published in 1907, listed 43 different medicinal preparations containing lithium (Merck 1907). The following year, the Sears, Roebuck, & Co. Catalogue advertised Schieffelin's Effervescent Lithia Tablets for a variety of afflictions (Sears 1908). These formulations were very popular, inspiring soft drink inventor Charles Leiper Grigg to create a new, "lithiated" beverage in 1929. Grigg called it "Bib-Label Lithiated Lemon-Lime Soda," and it was marketed for its potential to cure hangovers and lift mood (El-Mallakh 2007). This drink, better known to us today as 7-UP®, contained lithium citrate until 1950.

**Lithium is found naturally in food and water as a consequence of its presence in soil and bedrock. Lithium is found in trace amounts in most all life on the planet, including most plants and animals (Aral 2008, Anke 2005).**

Furthermore, the U.S. Environmental Protection Agency has estimated that the natural lithium intake of the average American adult ranges from approximately 0.65 to 3.0 mg per day (Saunders 1985). Drinking water is often a primary source of natural lithium, as are many grains, fruits, vegetables, meats and various types of seafood.

This information highlights a critical facet of lithium's story, which is crucial to bear in mind as we proceed to explore lithium's utility as an Alzheimer's intervention. Long before lithium was ever put into tinctures, pills, or tonic beverages, lithium was here, in nature. All life that has evolved on Earth has done so in the presence of lithium. Lithium has been and continues to be present in the ground we walk on, in the water we drink, and in the food we eat, as a potentially essential micronutrient helping us to cultivate good health.

The need for lithium in the human diet has been at the center of an occasionally spirited debate from various members of the medical and scientific communities. Over the past century, however, the march of research progress has been such that this debate has cooled significantly.

A body of empirical evidence suggests lithium's nutritional essentiality, revealing that this natural mineral may be required by humans and other mammals as a micronutrient that must be consumed regularly in trace amounts to maintain optimum health (Marshall 2015).

Based on this evidence, In 2002, an article published in the Journal of the American College of Nutrition suggested a provisional recommended daily allowance of 1 mg per day (Schrauzer 2002).

In modern medicine, lithium is most well known for its ability to stabilize mood. Lithium's efficacy has been repeatedly confirmed in research trials, making it the gold-standard intervention for bipolar disorder (Severus 2018). And thanks to its extensive use for bipolar, we have learned of its potential for treating cognitive decline and dementia.

## Lithium for Cognitive Decline: Early Evidence

It's been long known that bipolar disorder dramatically increases risks for dementia. As such, clinicians and researchers working with bipolar patients began to suspect that lithium may have effects beyond balancing mood when research analyses revealed that bipolar patients taking lithium had lower rates of dementia than did those taking other medications. In an attempt to validate this finding, one study compared Alzheimer's prevalence in elderly bipolar patients on chronic lithium therapy with similar patients who were not being treated with lithium (Nunes 2007). The results of their analysis were staggering: lithium therapy reduced the prevalence of Alzheimer's to levels observed in the general population, with just 5% of patients in the lithium group presenting with Alzheimer's as compared to 33% of the non-lithium group.

A research study conducted in Denmark evaluated the incidence of dementia in bipolar patients who were prescribed lithium. Longer intake of lithium was shown to reduce the risk of dementia to that of the standard population (Kessing 2008). This and other evidence has continued to inspire further analyses to this day, and in 2020 a new report was published documenting a reduction of dementia risk among bipolar patients taking lithium (Velosa 2020).

On the heels of such dramatic findings, scientists were eager to explore lithium's value as a direct treatment for dementia. Unfortunately, the first clinical trials of lithium ran headlong into the brick wall that has stymied pharmaceutical research for decades: attempting to treat patients who already have moderate to severe dementia. As Big Pharma has learned over and over again, there is little that can be done to correct brain damage in the advanced stages of Alzheimer's disease. Unsurprisingly, initial clinical trials with lithium for severe disease found little benefit.

In 2011, a groundbreaking research team set out to examine lithium's potential as a prophylactic (Forlenza 2011). In a study designed to determine whether long-term lithium treatment could prevent Alzheimer's in high-risk individuals, 45 subjects with mild cognitive impairment (a precursor to Alzheimer's) were randomized to receive lithium or placebo for one year. Over the course of the trial, lithium doses were less than the standard dosing for bipolar disorder to minimize the risk of side-effects. The researchers found that lithium reduced cognitive decline when compared to placebo and helped arrest other aspects of the disease process. Their overall conclusion was that lithium may have a significant impact on preventing Alzheimer's when administered in early stages of the disease.

## The Promise of Low-Dose Lithium

Evidence confirming the efficacy of low-dose lithium initially came from studies on lithium in groundwater. The research began uncovering stunning correlations between lithium levels and mental health. Since 1970, dozens of studies involving tens of millions of subjects have examined lithium levels in tap water from countries around the world—from Japan, Greece, and Lithuania to the U.K. and U.S.—and compared them to the incidence of health-related outcomes, such as rates of mental illness, psychiatric hospitalization, substance abuse, violent crime, and suicide (Schrauzer 1990, Ohgami 2009, Sugawara 2013, Shiotsuki 2016, Ando 2017, Shimodera 2018). A stunning majority of these (known colloquially as "the tap water studies") revealed significant associations, with higher lithium levels being protective.

Not only does this massive body of research underscore the legitimacy of lithium's nutritional essentiality but it also illuminates the promise of low-dose lithium.

As the tap water studies reveal, large doses of lithium are not necessary to support general health. It takes just trace levels of exposure from naturally occurring lithium to effect massive health benefits such as reduced rates of Alzheimer's, suicide, and mental health conditions.

This last point is crucial. While research with bipolar patients has generated some of the most robust evidence of lithium's protective attributes, it is limited by the potential side effects from the high doses used for bipolar treatment.

*All* trace elements, even essential ones, may be toxic in excess (Fraga 2005). Lithium is no different. At large, pharmacologic doses, lithium comes with some potential side-effects and can be toxic if dosages exceed prescribed amounts.

> *In safer trace quantities, however, lithium is a powerful promoter of health, an essential nutrient with a range of benefits that we are only now beginning to fully appreciate.*

Both animal and human studies have confirmed that lithium, when administered in this low, nutritional range, is very safe and generally well-tolerated. But is low-dose lithium effective when it comes to the treatment and prevention of cognitive decline?

In a landmark study, a scant 0.3 mg of lithium was administered once daily to Alzheimer's patients for 15 months (Nunes 2013). Subjects receiving lithium stabilized, while those in the control groups suffered progressive functional declines. Furthermore, the lithium treatment cohort began to realize gains in cognitive performance after about three months.

One of the more powerful arguments for low-dose lithium's therapeutic utility comes from a very recent study—a 2019 initiative to assess the potential benefits of long-term, low-dose lithium administration for patients in the beginning stages of cognitive decline (Forlenza 2019). Final analysis revealed that the placebo group worsened, while subjects treated with lithium remained stable over 2 years. Lithium treatment was associated with better performance on tests of memory and attention. Reflecting on these results, the scientists concluded that "Long-term lithium attenuates cognitive and functional decline in amnestic mild cognitive impairment."

## But How Does It Work? Key Neuroprotective Mechanisms

Not only is there a significant and still-growing body of evidence demonstrating that lithium is neuroprotective, but research has shed light onto the very mechanisms through which lithium confers such protection. Most significantly, lithium has been found to disrupt the key enzyme responsible for the deposition of amyloid plaques and neurofibrillary tangles—the biologic hallmarks of Alzheimer's. This enzyme is glycogen synthase kinase-3 (GSK-3), which normally plays a major role in neuronal growth and development.

In the healthy brain, GSK-3 is critically important, as it helps in the formation of memories (Duda 2018). In the Alzheimer's brain, however, GSK-3 becomes hyperactive in regions that control behavior and cognition. In this state, GSK-3 activates proteins that can damage brain cells—including amyloid-beta (Aβ) and tau (Sayas 2021).

Alzheimer's and other forms of dementia are primarily the result of two trademark lesions that occur at the cellular level: plaques and tangles. Plaques are formed by deposits of Aβ which eventually chokes off cell-to-cell communication in certain regions of the brain. Often simultaneously, other lesions called neurofibrillary tangles develop within brain cells. These tangles result from a disruption in the production of a protein called "tau."

Normally, tau filaments help to circulate nutrients and other essential molecules throughout cells. In Alzheimer's disease, however, these strands destabilize, becoming twisted or "tangled." Without a functional tau system to circulate vital compounds, brain cells starve and die. The result? The normal processes required for the creation, storage, and retrieval of memory are disrupted and cognition deteriorates.

When GSK-3 is overactive, these proteins, Aβ and tau, are produced faster than the processes that clear them, and they build up to form the signature plaques and tangles that disrupt brain function, causing progressive cognitive decline. Lithium functions as a direct GSK-3 inhibitor to prevent Aβ and tau overexpression, halting inappropriate amyloid production and tau activation before these proteins become problematic (Hampel 2019).

In addition to protecting the brain from the development of plaques and tangles, lithium has been shown to repair existing neuronal damage caused by Alzheimer's. For example, lithium ions encourage the synthesis and release of key nerve growth factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which in turn stimulate brain cell growth and repair (Young 2009). Imaging studies have shown that the brains of patients taking lithium have significantly higher gray matter volumes, suggesting that lithium has powerful stimulatory effects on processes relating to brain cell growth and development (Sun 2018).

Lithium's story certainly does not end here, and we likely have only scratched the surface as far as the mechanisms through which it supports the brain. Beyond promoting nerve growth factor production and inhibiting GSK-3, recent studies have confirmed that lithium influences certain cell receptors, protein synthesis and modification, genetic expression, cellular apoptosis (cell death), inflammatory mediators, glutamate excitotoxicity, immune cell activation, circadian rhythms, neurotransmitter activity and uptake…and the list continues to grow (Chiu 2010, Roux 2017).

**The more we learn about lithium, the more powerful the argument for its incorporation into Alzheimer's prevention strategies.**

### Lithium: Keystone of a Multifactorial Approach to Alzheimer's Treatment and Prevention

An impressive body of scientific research confirms that lithium bestows powerful protection through a multitude of mechanisms, many of which directly slow or inhibit the development of dementia. Furthermore, lithium has been shown to decrease levels of existing brain plaques and tangles - which for at-risk individuals is an enormously significant discovery.

In addition to its established efficacy as a protective agent, lithium's strong safety profile makes it a particularly attractive treatment, as prevention strategies for dementia are most effective when initiated early and continued over a long period of time. And it doesn't take a lot of lithium: studies have shown that lithium is effective in preventing age-related neurologic decline when used at safe "nutritional" or "low-dose" levels; studies have confirmed that low-dose lithium exerts measurable protective and cognition-enhancing effects (Kessing 2017, Nunes 2013, Nunes 2015).

Low-dose lithium offers one of the best strategies currently available to protect the brain from the devastation of diseases like Alzheimers. This strategy, in concert with other treatments shown to help in prevention, offers patients and medical practitioners worldwide legitimate hope that the tide of Alzheimer's, dementia, and cognitive decline can be turned.

## CHAPTER 3

# *A Multifactorial Approach: B-Vitamins, and Homocysteine Testing for Prevention*

Among the many reasons why standard pharmaceutical therapies for Alzheimer's fail is that they are generally designed to affect a singular aspect of the disease process. Research, however, has established that Alzheimer's (and other forms of cognitive decline) are incredibly complex, the outcome of dynamic interactions between numerous factors. While targeting one component might be helpful to a limited extent, addressing multiple pathways simultaneously is far more likely to elicit meaningful improvements in symptoms, or slow disease progression, when administered in early stages.

While a multifactorial approach to Alzheimer's is more challenging to implement than "one size fits all" pharmaceutical regimens, preliminary data has confirmed the therapeutic potential of this approach. In a case series of ten patients at various stages of

memory loss, a multifactorial treatment regimen (the Bredesen Protocol) was initiated that included diet and multiple supplements to address each patient's individual nutritional requirements (Bredesen 2014). Nine out of the ten subjects improved, with four returning to normal functioning. Only one subject continued to decline, an individual who entered the study with late-stage dementia—an advanced disease state likely too severe to respond to treatment.

The Bredesen Protocol is massively complex, a multifactorial approach geared towards treating numerous components that contribute to cognitive decline. Included in this protocol, however, are factors that are crucial to evaluate, including vitamin B12 and homocysteine. The analysis of these factors, simply and affordably accomplished via laboratory testing, should be included in *any* protocol to prevent or treat Alzheimer's, dementia, and cognitive decline.

## The B Vitamins (Vitamin B12, Folate and Vitamin B6) and Homocysteine

Checking vitamin B12 status and treating any identified deficiencies is crucial, not only as a component for the prevention of cognitive decline but also for the support and maintenance of general brain health.

Best known for its role in forming red blood cells, B12 works with vitamin B6 and vitamin B9 (folate) in the chemical pathways through which the neurotransmitters serotonin and dopamine are produced. Vitamin B12 is also critically important for the normal functioning of the nervous system, as well as the production and maintenance of myelin—the protective sheath around nerves. Deficiencies in B12 can cause myelin atrophy and degeneration, which if left untreated can lead to permanent nerve damage and pain.

When deficient, low levels of vitamin B12 are associated with numerous psychiatric and neurologic manifestations, including depression, mania, cognitive impairment, and psychosis (Lachner 2012).

In one study, it was reported that almost 30% of patients admitted to a psychiatric hospital had a deficiency of B12 (Ssonko 2014); in another, elderly women who were deficient in B12 were twice as likely to be depressed than those with normal levels (Penninx 2000).

Unfortunately, vitamin B12 deficiency has also established rather robust correlations with cognitive decline. A 2021 study in which 39,000 community-dwelling elders were assessed for vitamin B12 status revealed that low B12 was associated with poor attention, while severe B12 deficiency was found to be associated with poor immediate memory (Nalder 2021).

Numerous case reports of reversible dementia arising from vitamin B12 deficiency further confirm the B12—cognitive status link and underscore just how important B12 is for overall brain health (Ishida 2021, Huddar 2021, Brenes 2020, Silva 2019, Soysal 2018, Almoallim 2016). The sheer volume of such reports suggests something truly heartbreaking: many cases of reversible B12-deficiency dementia are likely being overlooked and untreated in the general population.

Unfortunately, vitamin B12 assessment is typically omitted from traditional diagnostic workups. The reasons why such omission is commonplace are likely numerous, but may stem from a simple assumption, that vitamin deficiencies simply don't exist anymore in the United States.

Research confirms this assumption to be categorically false.

A recent review confirmed metabolic B12 deficiency to be present in up to 40% of the population, with the researchers describing B12 deficiency as a commonly-missed contributing factor to cognitive decline (Spence 2016).

That a deficiency of an essential nutrient associated with severe nerve damage and dementia is being routinely omitted from diagnostic considerations in medicine is tragic. This tragedy is compounded by the fact that testing for B12 is simple, accessible, and affordable, as well as the fact that B12 supplementation can elicit profoundly positive changes for many patients...and not just those suffering cognitive decline.

It is important to note, again, that vitamin B12 often works synergistically with other members of the B-vitamin family. Folate and vitamin B6 are essential micronutrients that support healthy brain function, and both play critical roles in dementia prevention and treatment—especially as pertains to the neurotoxic amino acid homocysteine. Like B12, however, tests for folate and other B-vitamins are frequently omitted from diagnostic workups, despite solid evidence that deficiencies are not uncommon. Folate insufficiency, for example, is estimated to affect 20% of the general U.S. population and 19% of women of reproductive age (Pfeiffer 2019).

**Assessing vitamin B12, folate, and vitamin B6 status in patients, and addressing any deficiencies found to be present, is one of the most important components of an integrated approach to treating cognitive decline, as well as to support overall mental health.**

There are some special considerations that must be taken into account when approaching the assessment of vitamin B12. First among these is the fact that B12 levels that are considered "normal" may vary from laboratory to laboratory. Some labs list 200–1100 nanograms per liter (ng/L) as reflecting "normal" B12 status; others, levels between 150–400 ng/L are "normal." While this is obviously confusing, it is important to remember that all of these "normal" ranges have been derived from averages of large samples of "normal" individuals. The issue? Nutritional requirements can and often do vary significantly between individuals. A test result that lands within a lab's "normal" range is not the same as optimal.

This takes us to the second challenge inherent in B12 testing, which is that the serum B12 test, while often utilized as the primary means of quantifying B12 status, will only reveal B12 levels in the blood. What it will *not* reveal is how much vitamin B12 is available and circulating in the brain—which is where B12 is utilized for a range of vital processes. So, normal or even high serum B12 test results must be approached with a degree of caution and an understanding that the numbers do not necessarily reflect how much B12 is reaching the brain.

In a significant percentage of cases, serum B12 can be normal even in patients with marked deficiencies. Estimates suggest that up to 50% of serum results are incorrect (Stabler 2013). In some cases of cancer, liver disease, and/or kidney disease, serum B12 levels can be elevated while other indicators show signs of deficiency due to problems with uptake and utilization (Andrès 2013).

Testing for B12 deficiency should include a serum level, and even low-normal serum B12 (< 600 ng/L) should be treated. Due to the problems inherent with serum B12 testing, however, it can be helpful to investigate further. One additional test, checking homocysteine levels, can indicate additional needs for vitamin B12, along with vitamin B6 and folate.

Homocysteine is a toxic amino acid produced within the body. It is normally converted into other amino acids through enzymes dependent on vitamin B6, B12 and folate. High levels of this toxic amino acid indicate a need for more B vitamins.

*Normal or even high serum B12 test results must be approached with a degree of caution and an understanding that the numbers do not necessarily reflect how much B12 is reaching the brain.*

## Homocysteine

Numerous factors have been established as being tied to dementia risk - including lack of exercise, poor diet, disruptions in blood glucose, and obesity (Chen 2009). Research has also strongly implicated homocysteine, a toxic metabolite, with increased risk for cognitive decline and dementia (Smith 2018).

A neurotoxic amino acid known to damage brain cells, homocysteine is implicated in a number of pathologic conditions, including heart disease, osteoporosis, depression, schizophrenia, and kidney problems (Behere 2017, Bhatia 2015, Numata 2015, Clarke 2003). A growing body of research also links elevated homocysteine with neurological conditions, including memory loss, Parkinson's disease, and dementia (Isobe 2005, Nurk 2005). Clinical trials place the Population Attributable risk of dementia arising from excess homocysteine from between 4.3 to 31%; in other words, a person's risk of developing dementia may increase by up to a stunning 31% as a result of being in the upper quarter of homocysteine levels (Smith 2018). Other studies have concluded that high homocysteine may nearly *double* an individual's risk of progressive brain atrophy heralding Alzheimer's development (Seshadri 2002).

This is robust data, which casts light on a correlation that is anything but speculative. Quite the contrary, what has been dubbed "the homocysteine hypothesis" is based on the observation that dementia and Alzheimer's patients are consistently documented as having elevated homocysteine (Setién-Suero 2016, Hu 2016). In fact, a consensus statement was published in 2018 by an international group of experts who joined forces to affirm the validity of the homocysteine-dementia connection:

> *"We...conclude that elevated plasma total homocysteine is a modifiable risk factor for the development of cognitive decline, dementia, and Alzheimer's diseases in older persons (Smith 2018)."*

This acknowledgement, along with the vast body of research proving the dementia-homocysteine correlation is, in a way, tremendously encouraging: a definitive link between a toxic amino acid in the blood and brain atrophy points to a definitive protocol for intervention, a powerful strategy for modifying dementia risk.

High homocysteine levels can be diagnosed with a simple blood test and easily treated. If a patient's levels are high, supplementation with B12, folate, and vitamin B6 will reduce them.

## Mitigating the Risk of Cognitive Decline with B-Vitamins: Evidence

Studies have confirmed that increasing vitamin B levels reduces homocysteine and, by extension, the risk of related diseases such as Alzheimer's.

It is well known that mild cognitive decline and dementia are associated with brain atrophy (O'Brien 2001). Simply lowering homocysteine by taking vitamin B12, folate and vitamin B6 has been shown to slow the annual rate of atrophy by an average of 30% (Smith 2010). Additional documentation of B-vitamin protection against brain atrophy was achieved in a 2013 imaging study (Douaud 2013). Volunteers designated as "at-risk" for dementia were randomized to receive either a placebo or a B-vitamin formulation (folic acid, vitamin B12, and vitamin B6) for two years. Repeat brain imaging revealed that subjects taking the placebo showed an accelerated rate of atrophy in gray matter regions associated with Alzheimer's. Subjects given B vitamins, however, showed a significant reduction of atrophy in posterior brain regions, including the hippocampus.

Put simply, testing for homocysteine can be used as a functional marker for vitamin B12, folate and vitamin B6 status. Any case of elevated (> 12 µmol/L) or high normal homocysteine (9-12 µmol/L) should be addressed with supplemental B12, folate and B6. Boosting B vitamin intake can normalize a patient's homocysteine levels, thereby mitigating a primary risk factor for Alzheimer's disease. As written by the medical experts who together presented the 2018 International Consensus Statement, "…the public health significance of raised homocysteine … should not be underestimated, since it is easy, inexpensive, and safe to treat with B vitamins (Smith 2018)."

**High homocysteine levels can be diagnosed with a simple blood test and easily treated. If a patient's levels are high, supplementation with B12, folate, and vitamin B6 will reduce them.**

**High homocysteine may nearly double an individual's risk of progressive brain atrophy heralding Alzheimer's development (Seshadri 2002).**

CHAPTER 4

# *Fortifying the Nutritional Armor: Compounds Conferring Additional Protection*

Modern research, clinical observation, and ancient medicinal tradition together support the premise that a multifactorial approach to the treatment of cognitive decline is likely to elicit the best possible outcomes.

The cause of Alzheimer's is complex, involving multiple factors that interact along a dynamic continuum of potential risk. Accordingly, an approach in which several interventions are administered together may target the condition more effectively.

Available scientific evidence places low-dose lithium firmly in the center of a biologic model for the treatment and prevention of cognitive decline. While lithium is (rightfully) a keystone of this model, the model is further strengthened by the addition of natural compounds with other protective and restorative properties.

Here we will explore other natural products that do not require laboratory testing and hold great promise for the prevention and treatment of cognitive decline: curcumin, N-acetylcysteine, polyphenols and omega-3s.

## Curcumin

Curcumin is a polyphenol (more on polyphenols later) found in the roots of turmeric (*Curcuma longa*), the kitchen spice that gives curry its distinct, yellow-orange color. Turmeric root has been used as an herbal tonic for thousands of years and is revered in traditional systems of Ayurvedic medicine.

More recently, research exploring the medicinal applications of curcumin has surged. Curcumin is in fact one of the most extensively studied natural compounds; a simple search for "curcumin" on the National Library of Medicine database, turns up over 15,000 different research papers.

Clinical trials on curcumin have shown potential benefits of the compound in medical conditions ranging from inflammatory bowel disease, osteoarthritis, diabetes, and obesity to heart disease, autoimmune conditions,

and some types of cancer (Salehi 2019, Kunnumakkara 2017, Bhat 2019, Gupta 2013). Equal progress on understanding the therapeutic benefits of curcumin has been made in the psychiatric arena, particularly in regard to the treatment of depression.

A recent review found that curcumin appears to exert significant antidepressant benefits through multiple mechanisms (Zhang 2020). In rats, stress depletes "feel good" neurotransmitters such as serotonin; curcumin reverses this damage, thereby helping to normalize serotonin levels (Bhutani 2009). Evidence also suggests that curcumin confers antidepressant effects by increasing BDNF in different parts of the brain. A 2017 meta-analysis on curcumin's benefits for depression concluded that curcumin is "…safe, well-tolerated, and efficacious (Ng 2017)."

## Curcumin for Cognitive Decline: Biologic Mechanisms & Research Evidence

It is well established that curcumin is anti-inflammatory. In fact, it has some of the most potent anti-inflammatory properties of any plant compound. Studies have confirmed that curcumin suppresses proinflammatory pathways by inhibiting the synthesis of a number of inflammatory signalling molecules in different brain cells (Fadus 2016). Beyond anti-inflammatory effects, curcumin is also a powerful antioxidant (Ak 2008).

Bolstered by these and other findings illuminating curcumin's mechanisms of general protection, many researchers have sought to understand curcumin's direct impacts on the most notorious biologic hallmarks of dementia, including Aβ plaques and tau tangles. The question at hand then becomes: can curcumin combat pathologic cascades resulting in the accumulation of Aβ and/or tau? The latest research evidence suggests that the answer is yes.

Research in mice has shown that dietary curcumin can cross the blood-brain barrier and decrease the development of both plaques and tangles (Yang 2005, Ma 2009). Evidence from animal studies has also documented Aβ clearance from curcumin administration, with low doses of the compound decreasing Aβ by as much as 43-50% (Lim 2001).

From a functional standpoint, curcumin has been shown to prevent and reverse memory deficits in animal models of dementia (Agrawal 2010, Awasthi 2010, Samy 2016). A 2019 review of animal studies concluded that "...the vast majority of Alzheimer's disease animal models indicate that curcumin has both preventive and therapeutic effects on cognition." (Voulgaropoulou 2019)

## Curcumin for Cognitive Decline: Challenges in Application

As powerful as the health benefits of curcumin appear to be, curcumin's clinical utility is limited somewhat as a consequence of its poor gastrointestinal absorption. To counter these limitations, nutritional formulations often combine curcumin with other ingredients to enhance absorption and uptake.

It is my opinion that two formulations are standouts in this regard: Theracurmin® and Meriva®. These formulations have been carefully designed to facilitate absorption and to enhance the overall bioavailability of curcumin to maximize benefits.

## Theracurmin®

Theracurmin is proprietary curcumin formulation that mitigates absorption issues through an emulsification process. Curcumin is mixed with a natural gum, glycerin, and water, then ground and homogenized. The resulting product has been shown to be at least 27 times more bioavailable than standard curcumin extracts in both rats and humans (Sasaki 2011).

And the efficacy of the increased absorption of Theracurmin has been put to the test in clinical trials. In a 2014 study, Theracumin reduced pain scores among sufferers of knee arthritis by 62% over the course of an 8-week study, although reductions were only significant in patients with higher baseline levels of pain (Nakagawa 2014).

The benefits of Theracurmin have also been explored with regard to cognitive decline, and here we encounter some truly exciting data. In a study designed to assess the impact of daily Theracurmin administration on memory performance and the accumulation of brain plaques and tangles, 40 healthy subjects between the ages of 51 to 84 years were randomized to receive Theracurmin or placebo for 18 months. Data analysis revealed that Theracurmin use correlated with improvements in attention, as well as verbal and visual memory performance. Even more impressive, Imaging studies found decreases in plaques and tangles in brain regions that impact mood and memory (Small 2018).

### Meriva®

Meriva is a proprietary formulation in which curcumin is complexed with a compound called phosphatidylcholine to maximize overall absorption and bioavailability. Phosphatidylcholine is a phospholipid and a key structural constituent of cell membranes that has been shown to act as an emulsifying agent.

Studies have confirmed that the curcumin-phosphatidylcholine complex exhibits superior absorption and uptake. In animal studies, Meriva has been shown to increase blood levels around five times more effectively than curcumin alone, and a human trial found Meriva to be 29 times more bioavailable than standard curcumin (Cuomo 2011, Marczylo 2007).

As far as benefits, pilot studies and early clinical data have suggested that Meriva has a range of potential therapeutic applications. As a treatment for pain and inflammation, Meriva appears to benefit osteoarthritis, muscle soreness, and acute pain (Belcaro 2010, Di Pierro 2017, Di Pierro 2013). Clinical trials have also documented benefits for bone loss, benign prostatic hyperplasia, and a variety of eye conditions such as chronic diabetic macular edema and central serous chorioretinopathy (Riva 2017, Mazzolani 2018, Mazzolani 2013, Ledda 2012).

Inspired by the established anti-inflammatory properties of curcumin, some researchers have explored Meriva's clinical utility for the treatment of brain inflammation related to cognitive decline. A 2020 study in mice demonstrated that Meriva was able to reduce brain inflammation in a dose-dependent manner (Ullah 2020). These results are of great potential significance, as brain inflammation is widely regarded as a core component of Alzheimer's and Parkinson's disease.

Together, available data suggests that both Meriva and Theracurmin are reasonable choices to reduce brain inflammation underlying cognitive decline and dementia, and to support brain health through various protective mechanisms.

## N-Acetylcysteine (NAC)

NAC provides a more stable and bioavailable source of cysteine - the amino acid precursor of glutathione. As the primary antioxidant produced by the body, glutathione has powerful protective and health restorative properties. Along with the regeneration of the antioxidant vitamins C and E and the inhibition of various inflammatory cytokines, a key function of glutathione is the reduction of oxidative stress via the elimination of free radicals (Dean 2011).

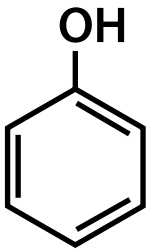
Evidence has been mounting that free radical damage is part of the core pathology of dementia, with studies demonstrating robust associations between dementia severity, increased oxidative stress, and decreased glutathione levels (Ansari 2010). Simultaneously, a growing body of literature establishes that NAC can effectively address and reduce free radical damage (Hara 2017).

Studies have documented the prevention of cognitive impairment with NAC in a mouse model of dementia (da Costa 2017). Additionally, rat studies have documented that NAC can mitigate cognitive impairments and ameliorate memory deficits induced by Aβ (Shahidi 2017). Together, these studies confirm NAC's potential as a treatment for Alzheimer's.

Human trials that included NAC as part of treatment for cognitive decline have also suggested benefits. A combination of NAC with B vitamins and other antioxidants has been shown to preserve cognition and maintain executive brain function. The effect size of treatment was robust, just under a large effect size based on the amount of improvement seen in patients (Remington 2015). The same formulation containing NAC was also tested in Alzheimer's patients directly. During the course of treatment, patients stabilized with no additional cognitive decline (Remington 2016).

In light of these findings, and in acknowledgement of NAC's excellent safety and tolerability profile, the healthcare establishment should be highly motivated to consider NAC as part of an approach for the treatment and prevention of cognitive decline.

## Polyphenols



**Phenol**

Polyphenols are a diverse group of phytochemicals derived from various plant species, many of which have been utilized medicinally for thousands of years. Some of the more common sources of supplemental polyphenols include grapes, blueberries, pine bark, and green tea.

From a biochemistry standpoint, the term "phenol" may refer to any member of a family of organic compounds characterized by a hydroxyl (OH) group attached to an aromatic six-carbon ring (see image). While discrepancies exist, *poly*phenols are generally defined as molecules containing two or more phenolic groups. Adding to the complexity, polyphenols are derived from one of two biochemical pathways in plants: the shikimate phenylpropanoid or the polyketide pathway. Polyphenols are also, by definition, devoid of nitrogen functional groups (Quideau 2011).

The research literature on the health benefits of polyphenols has been increasing, including findings that polyphenols improve aspects of mental health. What has come to light has largely confirmed polyphenols' long history of use in traditional herbal therapies, and has established promising new avenues for the promotion of cognitive health and the prevention of cognitive decline.

## Grape Polyphenols

Polyphenols derived from grapes and grape seeds are well known for their strong antioxidant effects (Sarkhosh-Khorasani 2021). Resveratrol is among the more well-known grape polyphenols, although grapes contain many other polyphenols including anthocyanins, flavanols, and flavonols (Xia 2010). In human clinical trials, grape polyphenols are often administered as grape juice.

Studies have shown that grape-derived polyphenols can boost cognitive performance. In a small 2010 trial exploring the cognitive effects of supplementation, grape juice was found to significantly improve verbal learning in older adults with memory decline (Krikorian 2010). Trial participants also experienced functional improvements in verbal and spatial recall, although this effect was not found to reach full clinical significance.

Building off these encouraging results, additional research further assessed the effects of grape juice on cognitive performance. In a 2012 trial, older adult participants with mild cognitive impairments were randomized to receive Concord grape juice or a placebo for 16 weeks and undergo routine assessments of memory function and brain activation (Krikorian 2012). The study found that participants who consumed grape juice displayed improvements in word recall on

memory tasks; furthermore, the grape-juice-treated subjects displayed relatively greater activation in the right side of the brain. The authors concluded that grape juice may enhance cognitive function in older adults with mild memory decline.

More recently, the cognitive benefits of polyphenols were explored in a study evaluating the effects of a combination of grape and blueberry extract on memory in healthy elderly subjects (Bensalem 2019). Among participants, there was a subgroup identified as having advanced cognitive decline at baseline. Those individuals with the worst baseline memory performance realized the most significant improvements from supplementation, suggesting that the extract helps to mitigate age-related episodic memory decline in people with the most serious impairments.

## Blueberry Polyphenols

While the body of research on the neurocognitive benefits of grape and grape seed is growing, research on blueberry polyphenols provides an additional body of evidence corroborating the potential cognitive benefits of these compounds.

In a 2018 trial designed to explore the effects of blueberry supplementation on regional brain activation in older adults at risk for dementia, subjects were randomized to receive placebo or blueberry powder for 16 weeks. Blueberry-treated subjects exhibited increased activation in several brain regions during memory tasks, although data analysis did not show any functional enhancement of memory performance (Boespflug 2018).

Other studies have yielded similar results. In one trial of healthy elderly subjects, blueberry supplementation was shown to increase blood flow and activation in brain regions related to cognitive performance, and was also correlated with improvements in working memory (Bowtell 2017). A separate study, in which healthy elderly individuals consumed one cup of blueberries a day as an experimental intervention, demonstrated an association between blueberry consumption and improvements in cognitive functioning (Miller 2018).

Results from one of the most recent studies on blueberry extract have also confirmed these findings. A 2018 trial assessed the effects of blueberry formulations on cognitive performance and other health parameters in older adults. Analysis revealed blueberry supplementation improved memory performance. Additionally, blueberry treatment was associated with heart health benefits with reductions in systolic blood pressure (Whyte 2018).

While there is certainly more for us to learn about blueberry polyphenols, and where these incredible plant compounds may fit into a modern therapeutic arsenal for cognitive decline, available research is incredibly encouraging. As concluded in a 2020 systematic review, blueberries appear to effectively improve aspects of cognition, although treatment standardization is necessary to allow for more comprehensive assessments of the effects of blueberry on discrete cognitive pathways and mechanisms (Travica 2020).

## Pine Bark Extract

The medicinal use of pine bark extends back to the days of ancient Greece, where physicians—including the renowned Hippocrates—used pine bark to treat inflammation (Simpson 2019). Modern-day scientific research has built upon this impressive tradition, and new studies have corroborated that the polyphenols found in pine bark have numerous potential applications across a variety of medical diagnoses and contexts.

Like other plant extracts containing polyphenols, pine bark extract has been shown to possess strong antioxidant and anti-inflammatory properties (Fan 2015). Studies have revealed that pine bark extract and other polyphenols can play pivotal roles in overall antioxidant activity—both within cells and systemically throughout the body (Packer 1999). These effects appear to have

real-world potential for treating or managing a number of conditions.

> *Pine bark extract has been documented as having therapeutic benefit for osteoarthritis, diabetes, high blood pressure, perimenopausal symptoms, attention deficit disorder, erectile dysfunction, heart disease, asthma, and cognitive function.*
>
> (Rohdewald 2018, Gulati 2015, Kohama 2013, Trebatická 2006, Trebatická 2019, Valls 2016, Belcaro 2011, Belcaro 2014).

In regard to general effects on brain health, pine bark polyphenols appear to possess protective properties. In cell cultures, pine bark extract has been shown to arrest free radical production induced by Aβ, effectively rescuing brain cells from death (Peng 2002). In a mouse model of dementia, Aβ levels were reduced and spatial memory was improved secondary to pine bark extract administration (Paarmann 2019).

Several human trials have also documented improvements in cognition associated with consumption of pine bark extracts. An early 2008 study demonstrated that pine bark extract, administered in tandem with the antioxidant vitamin C, significantly improved the response speed of spatial working memory and immediate recognition tasks in older male subjects (Pipingas 2008).

In a more recent trial designed to assess the effects of pine bark supplementation on mild cognitive dysfunction, subjects were randomized to receive pine bark extract with standard treatment or standard treatment alone. After 8 weeks, cognitive function improved 18% with the extract, whereas the average score of subjects treated with standard management did not (Hosoi 2018).

Alzheimer's and other forms of dementia are not the only conditions in which inflammation and increased free radical production in the brain are implicated. Traumatic brain injury (TBI) involves these components as well, and research has firmly established inflammation and oxidation as being linked to poorer outcomes in TBI cases. Here, too, pine bark extract has demonstrated therapeutic effects, as shown in a 2013 randomized controlled trial exploring the effects of pine bark on cognitive function in subjects with mild TBI. After six weeks of supplementation there was a reduction in self-reported cognitive failures. Improvements continued through week 11 and then stabilized (Theadom 2013).

Research suggests that even healthy individuals with no history of cognitive impairment may reap benefits from pine bark supplementation. A 2014 study showed pine bark extract to improve cognition and mood in healthy working professionals, and a 2015 trial demonstrated that pine bark extract improved not only cognitive performance but also reduced oxidative stress in older healthy subjects (Belcaro 2015; Belcaro 2014).

From a therapeutic standpoint, what we know thus far about pine bark extract is certainly enough to warrant its inclusion in a nutritional approach for the prevention and treatment of cognitive decline. Pine bark's millennia-old reputation as an anti-inflammatory and free-radical-reducing powerhouse has been emphatically substantiated, and we may reasonably expect breakthroughs about this phytochemical's effects to continue to emerge with ongoing research.

## Green Tea Extract

*"Man can do without food for three days, but without tea not for one."*
-Ancient Chinese proverb

The health benefits of tea have been known for thousands of years, and green tea has been celebrated as a health tonic by many cultures throughout the ages.

Like curcumin, grape seed, blueberry, and pine bark, tea is rich in polyphenols well known for their antioxidant and anti-inflammatory effects.

> *The body of modern research exploring the health benefits of tea is quite robust. Documented benefits of green tea include anti-inflammatory, anticancer, cardiovascular, immune modulating, anxiolytic, anti-diabetic, and potential anti-obesity effects (Tang 2019, Unno 2018).*

Evidence supports the premise that tea can improve symptoms of depression. On the scientific front, a 2015 meta-analysis of studies exploring the effects of tea consumption on depression found that for every three cups of tea consumed per day, depression risk decreased by 37% (Dong 2015). Some of tea's mood balancing effects may come from the synergistic action of tea polyphenols on brain-derived neurotrophic factor (BDNF)—the most prominent member of the class of nerve growth factors that promotes brain cell development, maturation, and survival. Even at very low concentrations, green tea polyphenols have been shown to increase BDNF activity (Gundimeda 2014).

The polyphenols found in tea are presumed to underlie a majority of its medicinal properties. Most polyphenols found in tea are different forms of catechins—members of the flavonoid chemical family and secondary metabolites in certain plants. Of catechins present in green tea, epigallocatechin gallate (ECGC) is by far the most well-researched, having received significant attention from the scientific community.

Among myriad other health benefits, tea has long been recognized as a natural source of antioxidants, and recent studies have confirmed that tea polyphenols exert powerful antioxidant effects (Teixeira 2021). Coupled with tea's celebrated history of use in traditional systems of medicine, these new studies have sparked great interest in tea's potential viability as a treatment for Alzheimer's, dementia, and cognitive decline. A 2019 meta-analysis of observational studies examining associations between dementia and green tea consumption concluded that green tea intake may reduce the risk for dementia, Alzheimer's, and cognitive impairment (Kakutani 2019).

A more recent study exploring tea consumption and cognitive health in Chinese adults also found benefits. The analysis of tea consumption revealed that habitual and high-frequency tea intake was associated with a lower risk of cognitive impairment (Zhang 2020).

Of relevance to Alzheimer's and other dementias, green tea appears to protect brain cells from the ravages of Aβ (Haque 2008). Lipopolysaccharide (LPS) is an inflammatory molecule from bacteria. When LPS is injected into mice it can precipitate memory problems, brain inflammation, and Aβ production. A 2013 experiment demonstrated that ECGC was able to prevent cognitive problems and hyperinflammation, while inhibiting Aβ production caused by LPS in rodents (Lee 2013).

Again, we find the body of modern research literature corroborating ancient medicinal wisdom, illuminating yet another promising avenue—tea consumption and supplementation—towards the refinement of a nutritional model for Alzheimer's prevention.

## Omega-3 Fatty Acids

The importance of dietary fat and essential fatty acids (EFAs) in maintaining brain health cannot be overstated. Although dietary fat has been much maligned over the years, it remains an unequivocal scientific and medical fact that essential fats are necessary for the proper functioning of the brain.

**Every aspect of cellular communication, cell membrane integrity, and cell membrane functioning depends *absolutely* on the availability of essential lipids. In addition, these fats play a significant role in reducing inflammation throughout the body (Poles 2021).**

Every membrane of every cell in the human body is made from fat. Likewise, each cell in the body relies on EFAs for a variety of functions, including the manufacture and repair of these membranes and neurotransmitter function. Cell membrane health, which is entirely dependent upon the availability of EFAs, is also critical for the cellular uptake of nutrients; accordingly, a deficiency of EFAs may actually worsen a patient's overall nutritional status, as structurally compromised membranes will inhibit uptake of nutrients (Smit 2004).

Beyond the roles they play in supporting the health of individual cells, fats also play crucial roles in the brain, a fact which is reflected in the brain's very composition. Upwards of 60% of the dry weight of the human brain is fat, with approximately 15% being the EFA docosahexaenoic acid (DHA) (O'Brien 1965, Fraser 2010).

## Omega-3s: A Review

A healthy body with sufficient levels of vitamins, minerals, and amino acids can synthesize many of the fatty acids that it needs to maintain health. However, there are two classes of polyunsaturated fatty acids that the body cannot produce, and must therefore acquire through diet (hence their designation as "essential"). One class is the omega-3 fatty acids.

**Upwards of 60% of the dry weight of the human brain is fat, with approximately 15% being the EFA docosahexaenoic acid (DHA) (O'Brien 1965, Fraser 2010).**

There are three major types of omega-3 fatty acids:

- Alpha-linolenic acid (ALA), found primarily in plants such as flax, chia, walnuts, pumpkin seeds, and other sources
- Eicosapentaenoic acid (EPA), found primarily in seafood
- Docosahexaenoic acid (DHA), found primarily in seafood

The body can manufacture both EPA and DHA from ALA, but the rate of conversion is low, and the conversion process susceptible to deficiencies of cofactors that support enzymatic reactions (Brenna 2009). Direct consumption of EPA and DHA is always preferable for treating deficiencies, as direct intake improves levels more quickly.

Unfortunately, omega-3 deficiency is very common. The authors of a recent global study involving the assessment of omega-3 levels in healthy adults concluded that "...the very low to low range of blood EPA + DHA for most of the world may increase global risk for chronic disease." (Stark 2016).

## Omega-3 Deficiency: Implications for Health

A deficiency of omega-3 fatty acids is associated with a number of adverse mental health outcomes. These fats appear critical for neurotransmitter function of both serotonin and dopamine (Patrick 2015, Healy-Stoffel 2018). Research in mice has found that omega-3 deficiency increases the stress response and leads to direct damage and atrophy of specific brain cells, likely contributing to the development of depression (Larrieu 2016, Larrieu 2014).

One of the primary omega-3 fats found in the brain, DHA can make up 14% to 17% of gray matter and is involved in various aspects of brain cell communication (Bradbury 2011, Skinner 1993). While found in lower levels, EPA is still heavily involved in brain function.

Experimental studies have revealed that EPA enhances the release of serotonin, and has more potent anti-inflammatory effects than DHA (Patrick 2015, Su 2015).

In addition to their effects on serotonin, omega-3 fats appear to influence BDNF production. In a study of schizophrenic patients, supplementation with fish oil was found to increase subjects' BDNF which correlated with improvements in patients' depressive symptoms (Pawelczyk 2019).

## Omega-3s and Cognitive Decline

In consideration of the critically essential roles that omega-3 fatty acids play in so many aspects of brain health, it should come as little surprise that research has confirmed that dementia is correlated with omega-3 deficiency.

A 2021 investigation of relationships between essential fatty acid levels (omega-3s and omega-6s) and dementia collected data from 1,264 participants. Analysis revealed that higher levels of EPA were associated with a lower incidence of Alzheimer's as well as a decreased risk for dementia among those with an increased genetic risk for the condition (Melo van Lent 2021).

Studies examining dietary intake of concentrated omega-3 sources have also found correlations between omega-3 consumption and cognitive outcomes. Fish has long since been established as one of the richest natural sources of dietary EFAs. A 2018 meta-analysis found that those consuming greater amounts of fish had their risk for Alzheimer's disease reduced by one-third (Bakre 2018).

Given the consistency with which research has demonstrated correlations between dietary omega-3 intake and Alzheimer's disease, some research has gravitated towards analyzing the therapeutic effects of omega-3 supplementation. Overall, the effects of omega-3 supplementation on cognitive outcomes in randomized clinical trials have been mixed, although results trend positive (Marti Del Moral 2019, Yassine 2017).

A meta-analysis of trials using fish oil for cognitive decline concluded that:

> *"...omega-3 supplementation might have a positive effect on cognitive function. Thus, omega-3...fatty acids could be used as a preventive or therapeutic tool for cognitive decline in aged or elder adults (Moral 2019)."*

Based on the available data, consumption of omega-3-rich food sources and supplementation with omega-3 fatty acids is recommended as a means to support long-term brain health. In fact, the American Psychiatric Association recommends that everyone eat at least two servings of fatty fish per week (Tanskanen 2000).

## Omega-3 Supplementation

Omega-3 fats protect the structural integrity of the brain and reduce inflammatory damage. EPA appears to have more robust mental health benefits than DHA, so combination products with an EPA:DHA ratio greater than two are usually recommended. When choosing a product, it is important to verify that it is free of contaminants, and not oxidized or rancid since fish easily accumulate toxins and fish oil is highly susceptible to spoilage. Due to these issues, better quality fish oil should display proof of independent lab testing implemented by the manufacturer to consistently check for contaminants and product stability.

# *Treatment Protocol*

The current trajectory of the Alzheimer's crisis is simply unacceptable—not only in terms of its scope but also in terms of the dismissal of research-supported evidence for prevention. While drug-based therapies reduce symptoms transiently, they do not change the course of the disease.

That the paradigm must be flipped is obvious. It is equally as obvious that the protection and maintenance of neurologic health needs to be initiated early, through the use of nutrients that target critical pathways in the brain...supporting healthy function, protecting against free radicals and inflammation, and inhibiting the development of plaques and tangles throughout the brain. Prevention opens the door to sustained health, and an answer to the challenge of Alzheimer's disease.

All the interventions detailed in this book are supported by published evidence as being capable of altering the course of dementia. These are not patentable drugs but rather nutrients and natural phytochemical constituents with protective, restorative, and cognition-optimizing properties. In combination, these interventions offer some of the best hope for arresting the progression of cognitive decline and reversing the dementia epidemic itself.

Wellness is, of course, more than just biochemistry. Science has long since established that environmental and lifestyle factors influence brain health and overall risk of cognitive decline. A comprehensive approach to the prevention of dementia should therefore be inclusive of lifestyle modifications that support mental wellness. A diet that eliminates most processed foods, is low in sugar and simple carbs, high in vegetables, quality protein and healthy fats is instrumental. Staying physically, mentally, and socially active is also key, as are techniques for stress reduction such as yoga, meditation, and mindfulness.

As physical and mental health go hand in hand, so too do nutritional and lifestyle approaches for the preservation of healthy cognitive function. Dietary changes, exercise routines, and mindfulness or meditation practices can easily be implemented in tandem with regimens of nutritional supplementation to enhance overall wellbeing.

## COST-EFFECTIVE STRATEGIES FOR MITIGATING BIOCHEMICAL RISK FACTORS FOR COGNITIVE DECLINE

| Supplementation | |
|---|---|
| **Luma TC** | 1-2 tabs daily with food |
| **CurcumaSorb Mind** | 2 caps daily with food |
| **Fish Oil** | 2000-3000 mg daily with food |

## STRATEGIES FOR OPTIMIZING OVERALL PHYSICAL & PSYCHOLOGICAL WELLNESS

| Lifestyle | |
|---|---|
| **Diet** | Higher in plant foods, healthy protein, and fat; lower in processed foods and sugar |
| **Exercise** | Regular exercise as part of a daily routine |
| **Stay Mentally Active** | Including work or hobbies, learning a new language or other skills |
| **Stress Reduction** | Meditation, yoga, tai chi, or other stress-reducing activities |
| **Stay Social** | Make sure your social network supports healthy behaviors |

**Prevention opens the door to sustained health, and an answer to the challenge of Alzheimer's disease.**

# Supplementation

## Luma TC

Luma TC is a proprietary supplement formulation that is classified as a "medical food." While unfamiliar to many, medical foods are a designation of the U.S. Food and Drug Administration (FDA) occupying a category that straddles the divide between nutritional supplements and pharmaceuticals. According to the FDA, a medical food is "...a food which is formulated to be consumed...under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." (CfFS 2020)

As a medical food, Luma TC is "...clinically proven to synergistically address the multi-factorial cellular pathology of the Alzheimer's disease process" (Luma TC 2021). The ingredients in Luma TC include Theracurmin, lithium orotate, N-acetylcysteine, folate (as methylfolate), vitamin B6 and vitamin B12 (as methylcobalamin).

For a complete list of ingredients in Luma TC, please refer to page 28.

## CurcumaSorb Mind

CurcumaSorb Mind is a product from Pure Encapsulations that combines the therapeutic powers of curcumin with additional polyphenols from grape, blueberry, pine bark and tea. This synergistic combination can act as a potent antioxidant and anti-inflammatory to help protect, preserve, and restore neurological function.

For a complete list of ingredients in CurcumaSorb Mind, please refer to page 28.

The scope of the Alzheimer's disease epidemic is staggering, and getting progressively worse. Cases have tracked steadily upwards over the last several years as pessimism from within the medical community has swelled. Each failed pharmaceutical drug trial in the search for an Alzheimer's cure is another weight stacked against hope. Progress and failure march to an increasingly rapid drumbeat as Alzheimer's diagnoses are now charted in seconds, and while Big Pharma persists in funneling billions into efforts to find a magic bullet fix, the human costs of Alzheimer's, dementia, and cognitive decline remain simply unfathomable.

The picture is grim, but it does not have to be our destiny.

Having spent decades practicing psychiatry in accordance with a systems neurobiology model, my perspective remains grounded in the idea that diseases arise from nutritional and genetic imbalances.

**Scientific research continues to deliver unequivocal confirmations of the basic laws of human biology—that dietary intake, environmental factors, and lifestyle habits are powerful determinants of physical and mental health, and that internal or external disruptions can impact biologic function and potentially contribute to the emergence or entrenchment of a disease state.**

The identification of such factors, and of the mechanisms through which they impact brain function, is not simply an academic exercise. On the contrary, each nutritional, environmental, and/or lifestyle variable established to be a modifiable risk factor for Alzheimer's represents another tool for the prevention of Alzheimer's placed in our therapeutic arsenal.

## Opening the Therapeutic Toolbox: Answers to Alzheimer's & Cognitive Decline

It is my hope that this book will serve as a guide, establishing an evidence-based foundation from which effective strategies may be formulated for the prevention of Alzheimer's, dementia, and cognitive decline. If implemented, these strategies, inclusive of nutritional and phytochemical interventions, may well usher in a new era in neurologic medicine: an era in which there *are* answers to cognitive decline, and in which Alzheimer's is neither a foregone conclusion nor a death sentence.

**The research clearly demonstrates that the tools with which we may realize a turning of the Alzheimer's tide are available to us, right now—it's simply a question of using them.** The nutrients and herbal constituents detailed in this book are proven to confer measurable benefits upon cognition, memory and many other discrete parameters of brain health. Many have also been shown to combat biochemical processes established to be key factors in the development of dementia. Used appropriately, they are safe and effective; used *together*, they coalesce a powerful rebuttal to the pathologic cascades underlying Alzheimer's and present today's clinicians with a stunning opportunity.

Through the implementation of a new, nutritionally oriented model of prevention, we have before us a chance to rewrite the Alzheimer's narrative. We can cling to ineffective symptom suppression measures, or we can place humankind in the drivers' seat of mental wellness—each of us masters of our own neurologic destiny—and reduce immeasurable levels of suffering worldwide from neurodegenerative disease.

We have sought an answer to the Alzheimer's epidemic, and have found not one answer but many. We have the tools. The time to act is now.

## Alzheimer's Risk Factors Suggesting the Need for Prevention:

*(taken with permission from lumatc.com)*

- **Age 40 or above** - Silently in our 40's nerve cell deterioration can begin to occur in our brain. This "preclinical stage" is the time for prevention.
- **Age 65 or older** - Age is the biggest risk factor for Alzheimer's, doubling over 65.
- **Gender** - There are twice as many women as men over 65 with Alzheimer's disease.
- **Genetic Factors** - APOE-4 is the strongest genetic risk factor for Alzheimer's disease, MTHFR Polymorphism is a risk factor for AD. To find out your risk, call DVD 985-629-5742 for these genetic tests.
- **Family history** - Cognitive impairment, memory loss, dementia, Alzheimer's, Parkinson's, Huntington's, or ALS.
- **Homocysteine levels over 11 mol/L** - One of the factors that has been implicated in affecting the rate of brain atrophy is high levels of an amino acid called homocysteine. Studies show that raised levels increase the risk of Alzheimer's disease by 50%. Call your doctor for a test.
- **Mental state** - History of depression, bipolar disorder, loneliness, seclusion or fear of aging.
- **Diabetes** - Diabetes can cause several complications, such as damage to your blood vessels. Many people with diabetes have brain changes that are hallmarks of both Alzheimer's disease and vascular dementia.
- **Previous head trauma** - Over the past 30 years, research has linked moderate and severe traumatic brain injury to a greater risk of developing Alzheimer's disease or other types of dementia years after the original head injury.
- **Lack of exercise** - Physical activity benefits the brain. Studies show people who are physically active are less likely to experience a decline in their mental function.
- **Moderate to heavy alcohol or tobacco use** - People who smoke a pack of cigarettes or more a day develop Alzheimer's disease years earlier than those who do not, and heavy drinking of alcohol increases the risk even more.
- **Cardiovascular issues** - Hypertension, stroke, high cholesterol or obesity.
- **Toxic and chemical exposure** - Heavy metals such as lead, mercury, arsenic, cadmium, pesticides or insecticides.

> *"The neuropathological processes of Alzheimer's disease occur up to **twenty** years before clinical symptoms of the disease. Analysis of brain amyloid imaging and cerebrospinal fluid biomarkers demonstrate early deposition of amyloid in individuals with known risk factors. These findings raise the possibility of preventing clinical symptoms!!!"*[1]

1. Alzheimer's Disease Genetic Risk Factor APOE-4 Also Affects Normal Brain Function, Georgetown U., Current Alzheimer Research, 2016

## Luma TC – active ingredients

| | |
|---|---|
| TC (Theracurmin) Sub-Micron Particle Curcumin | 180mg |
| Lithium Orotate | 5mg |
| N-Acetyl Cysteine | 300mg |
| L-Methylfolate Calcium | 500mcg |
| Methylcobalamin (B12) | 50mcg |
| Pyridoxal-5-Phosphate (B6) | 5mg |

LumaTC.com. Ingredients. Lumatc.com.