Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

2-Hydroxybenzylamine

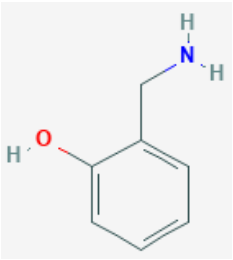
Evidence Summary

It protects against cellular damage by scavenging reactive carbonyl species. It is safe, and may protect against age-related pathologies when used prophylactically, but it cannot reverse pre-existing damage.

Neuroprotective Benefit: It may protect against cognitive decline stemming from neuronal damage associated with increasing brain lipid oxidation with age.

Aging and related health concerns: It may protect against cardiovascular pathology by preventing protein dysfunction and inflammation associated with reactive carbonyl species, and may reduce risk for some gastrointestinal cancers.

Safety: It has been well-tolerated with no evidence of drug-related adverse events in Phase 1 trials in healthy adults and in animals treated for several months. The effects of chronic use in humans still need to be characterized.

Availability: OTC (supplement) and in clinical trials (drug)	**Dose**: Administered as oral capsules. The therapeutic dose has not yet been established. Most trials test doses of 500 mg 3x/day (TID) or 750 mg TID. OTC supplements recommend a dose of 100 to 200 mg per day.	**Chemical formula:** C_7H_9NO **MW**: 123.15 g/mol  Source: PubChem
Half-life: 2-3 hours (effective $T_{1/2}$ ~ 4-5 hours with multiple dosing)	**BBB**: Penetrant	
Clinical trials: Phase 1 SAD and MAD trials in healthy young adults (n=18; n=18), older adults (n=18), and a CSF study (n=3). A Phase 2 trial in atrial fibrillation (n=89) ended early. Phase 2 trials in RA (~n=32) and familial hypercholesterolemia (~n=72) are ongoing.	**Observational studies**: Reactive carbonyl species (γ-ketoaldehydes) increase in the brain in AD, in the vasculature with hypertension, and in gastrointestinal cancer tissue.	

What is it?

2-Hydroxybenzylamine (2-HOBA, also called salicylamine and 2-aminomethylphenol) is a phytonutrient derived from buckwheat [1]. 2-HOBA acts as a scavenger of some types of reactive carbonyl species, including γ-ketoaldehydes.

Oxidative stress can drive the peroxidation of polyunsaturated fatty acids, which can then undergo rearrangements to form reactive carbonyl species, which then exert damage by forming covalent modifications on proteins, nucleic acids, and phospholipids. They can also promote the formation of advanced glycation end products (AGEs). These modifications can cause mutations, alter function, and inhibit the efficient degradation of these damaged cellular components. Reactive carbonyl species have higher potential to elicit cell damage relative to reactive oxygen species (ROS), due to their stability, longer half-life, and ability to traverse membranes.

Different types of reactive carbonyl species modify different functional groups, therefore certain classes of scavengers may be better suited toward certain diseases than others, or a combination may be needed to achieve clinical efficacy. The two main classes of reactive carbonyl species scavengers are

thiols and amines, and they tend to scavenge different types of reactive carbonyl species. γ-ketoaldehydes, which include isoketals, isolevuoglandins, and neuroketals, are the most highly reactive, and are strongly pro-inflammatory. Since they react with primary amines, they are effectively scavenged by amine-based scavengers like 2-HOBA. Malondialdehyde (MDA), which is one of the most abundant lipid peroxidation products, is also effectively scavenged by 2-HOBA. Meanwhile, other damaging species, including 4-HNE and acrolein are more effectively scavenged by thiols [1].
The vitamin B6 vitamer pyridoxamine was identified as an amine-based scavenger of reactive aldehydes in a screen [2]. A structure-function analysis of analog compounds identified buckwheat-derived 2-HOBA as a lipophilic structural analog that acts as a far more potent scavenger of reactive aldehydes, without retaining other major physiological activities of the vitamer.
The scavengers act as nucleophiles and compete with endogenous nucleophilic targets, therefore they must have high potency and be highly bioavailable in tissues to effectively outcompete. 2-HOBA is able to scavenge γ-ketoaldehydes 1,000-fold faster than the rate of reaction with lysine residues on endogenous proteins [3]. Therefore, it can effectively prevent the formation of protein adducts, which are associated with a variety of age-related diseases.
2-HOBA is currently marketed as a dietary supplement by TSI Health Sciences, while a higher concentration formulation is being developed as a pharmaceutical by MTI Biotech, a subsidiary of TSI. 2-HOBA has been tested in Phase 1 trials for safety and is being tested in Phase 2 trials for other indications, including atrial fibrillation, familial hypercholesterolemia, and rheumatoid arthritis.

Neuroprotective Benefit: It may protect against cognitive decline stemming from neuronal damage associated with increasing brain lipid oxidation with age.

Types of evidence:

- 1 small trial assessing the BBB penetrance of 2-HOBA
- 5 observational studies (Peroxidized lipids content in AD brain and CSF, Reactive carbonyl species content in AD brain)
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

There have not been any studies directly testing whether 2-HOBA can prevent cognitive decline, but observational studies indicate that reactive carbonyl species are elevated in the Alzheimer's disease (AD) brain, and may contribute to cognitive decline.

The lipidome of the human brain undergoes progressive changes during aging starting around age 50 to 55 [4]. Some areas, such as the prefrontal cortex, have a high level of polyunsaturated fatty acids, including arachidonic acid and docosahexaenoic acid (DHA), which are susceptible to lipid peroxidation [5]. The oxidation of these polyunsaturated fatty acids leads to the formation of highly reactive γ-ketoaldehydes. The oxidization of arachidonic acid results in isoketals, while the oxidation of DHA creates neuroketals. These pathogenic peroxidized lipids are reactive carbonyl species that induce damage by modifying proteins and nucleic acids. During aging there is an increase in the level of lipid oxidation and associated protein damage in the human brain, though some regions are more resistant than others.

In the context of healthy aging, the brain lipid profile is largely resistant to change, however, in the context of Alzheimer's disease there appears to be an accumulation of oxidized lipids and reactive carbonyl species [5]. Isoprostanes and neuroprostanes, are precursors to isoketals, and neuroketals, respectively, and markers of lipid peroxidation. Free F4-neuroprostanes were found to be increased in the CSF of AD patients [6], while bound F4-neuroprostanes were increased in the occipital and temporal cortices of AD patients [7]. There is also evidence for a lower reducing capacity in the AD brain, which may underlie the increase in free radical damage to DHA in the cerebrum [8]. In these studies, the levels of neuroprostanes did not correlate with plaques or tangle pathology. However, levels of isoketal or neuroketal protein adducts (i.e. associated protein damage) did correlate with AD pathology [9]. The isoketal adduct, levuglandin-lysine lactam was found to be 12.2-fold higher in the AD brain (n=7) relative to age-matched controls (n=5), and positively correlated with Braak stage ($r=0.92$, $P<0.0001$) [9]. Neuroketal adducts were found to be elevated in the hippocampus in a separate study (n=6 AD, n=6 age-matched controls), preferentially localized to hippocampal pyramidal neurons, and were found at 5-fold higher than isoketal adducts [10].

γ-ketoaldehydes are also highly pro-inflammatory, thus they can promote both oxidative stress damage and inflammation. The elevation in γ-ketoaldehydes in AD could lead to the modification of proteins essential for neurotransmission and neuronal function, thereby promoting the mechanisms associated with cognitive decline. Therefore, compounds which can scavenge γ-ketoaldehydes could potentially protect against age-related and AD-associated cognitive decline.

One emerging hypothesis regarding the etiology of AD suggests that it has features of an autoimmune disease [11]. The formation of reactive carbonyl protein adducts has been associated with the formation of immune activating neoantigens in other conditions/model systems, such as hypertension [12]. Thus, the formation of these adducts in the brain may also induce pathological neuroinflammation and neurodegeneration, which could potentially be prevented through the use of scavengers, like 2-HOBA.

A small study (NCT03554096) including three participants (age 50 ± 9 years) assessed 2-HOBA levels in the CSF via lumbar puncture taken 90 minutes following the administration of a single oral dose of 550 mg of 2-HOBA acetate. 2-HOBA was detectable in the CSF, and reached an average concentration of 462 ± 327 ng/ml, which corresponded to 34–74% of the level of 2-HOBA in the plasma. There was no appreciable metabolism of 2-HOBA in the brain, as levels of its primary metabolite, salicylic acid, only reached 0.5–1.7% of plasma levels.

***Human research to suggest benefits to patients with dementia*:**

There is a planned randomized, double-blind, placebo-controlled, dose-finding Phase 1b/2a trial testing 2-HOBA at doses of 250, 500, or 750 mg TID for 16 weeks in patients with mild cognitive impairment or early AD (NCT06432166).

***Mechanisms of action for neuroprotection identified from laboratory and clinical research*:**

Reactive carbonyl scavengers, such as 2-HOBA, are likely to be most effective at early stages to slow disease progression, or as a preventative to delay disease onset by reducing oxidative stress mediated cellular damage.

Alzheimer's disease: POTENTIAL BENEFIT WITH EARLY INTERVENTION (preclinical)
Highly reactive γ-ketoaldehydes, such as levuglandins, have been shown to accelerate the formation of Aβ42 oligomers, and enhance their neurotoxicity in cell culture [13]. Modification of proteins by γ-ketoaldehydes can also inhibit their clearance by the proteasome [14]. Therefore, it is hypothesized that γ-ketoaldehyde scavengers could protect against neurodegeneration in AD.
2-HOBA treatment (1 g/L in drinking water) starting at 4 months of age was protective against deficits in spatial working memory at age 12 to 14 months, based on performance on the radial arm maze, in mice

expressing human ApoE4 [10]. However, 2-HOBA had no effect on age-related motor deficits in these transgenic animals.

Seizure-associated cognitive impairment: POTENTIAL BENEFIT (preclinical)
Highly reactive carbonyl species, γ-ketoaldehydes, were found to be elevated in the hippocampus and perirhinal cortex following epileptogenic injury in the kainic acid and pilocarpine-induced temporal lobe epilepsy mouse models [15]. Treatment with 2-HOBA (200 mg/kg i.p. 30 min after seizure-inducing agent + 1 g/L in drinking water) reduced the formation of γ-ketoaldehyde adducts, leading to a corresponding reduction in seizure-induced spatial and reference memory deficits. 2-HOBA protected against neuron loss, but had no effect on seizure induction.

***APOE4 interactions*:** Unknown

Aging and related health concerns: It may protect against cardiovascular pathology by preventing protein dysfunction and inflammation associated with reactive carbonyl species, and may reduce risk for some gastrointestinal cancers.

Types of evidence:

- 1 biomarker analysis from 2 RCTs
- 6 observational studies (Isoprostane, isoketal, isoLG levels)
- Several laboratory studies

Lifespan: EXTENSION OF MEDIAN LIFESPAN IN WORMS
Carbonyl stress is thought to be a contributing factor to age-related pathology [16]. Reactive carbonyls, such as isoketals, can contribute to molecular aging by reacting with proteins, leading to chemical modifications that can inactivate or alter the activity of the protein targets. As an effective isoketal scavenger, 2-HOBA can prevent the formation of these protein adducts, thus preserving protein function. 2-HOBA treatment was found to extend the lifespan and healthspan of *C. elegans* through the preservation of Sirtuin (SIR2.1) function, and enhancing resistance to oxidative stress damage in mitochondria [17]. Worms treated with 2-HOBA beginning at the start of adulthood had dose dependent increases in median lifespan, with worms treated at the highest dose (500 uM) experiencing a 56% increase in median lifespan (from 16 to 25 days). Treated worms also showed improvements in

healthspan based on a dose-dependent decrease in lipofuscin granule accumulation and slowing of the decline in pharyngeal pumping rate.

Immune function: 2-HOBA HAS IMMUNOMODULATORY EFFECTS

Aging is associated with increased chronic inflammation and decreased productive immune responses. The accumulation of oxidative stress damage may contribute to this dysfunctional immune profile. The impact of 2-HOBA on immune function was assessed as part of the analysis of blood samples collected during two Phase 1 trials including healthy young adults (n=17; average age 33.8 ± 12.6) and healthy older adults (n=16; average age 66.1 ± 4.3) [18]. Participants received placebo or 2-HOBA acetate at a dose of 500 or 750 mg TID, corresponding to 336 and 504 mg 2-HOBA, respectively. Doses of 2-HOBA acetate were administered as (two or three) 250 mg capsules every eight hours, with treatment lasting for 14 days. Plasma samples were collected at baseline and 120 minutes after the last dose. Since 2-HOBA exposure was found to be similar for the two doses in this study, the analysis compared the combined 2-HOBA group with placebo. Changes in blood-based oxidative stress and inflammatory biomarkers were assessed using the Olink® targeted inflammation panel. Fifteen immune-related chemokines and cytokines were differentially expressed in response to 2-HOBA. CCL19, IL-12β, IL-20Rα, and TNFβ were found to be increased following 2-HOBA, relative to placebo, while levels of TWEAK, a leukocyte expressed protein associated with inflammation, fibrosis, and angiogenesis, were reduced with 2-HOBA. This small, preliminary study suggests that 2-HOBA has immunomodulatory properties, but it remains to be established whether these changes have clinically meaningful effects on chronic inflammation, pathogen control, or other functional immune-related parameters.

Cardiovascular disease: POTENTIAL BENEFIT (preclinical)

Reactive carbonyl species are major mediators of oxidative stress damage [19]. They form irreversible modifications to proteins, leading to protein dysfunction and the activation of the immune system. Studies suggest that oxidative stress promotes the formation of reactive isoketals, which modifies proteins in a manner that activates the immune system and drives vascular pathology. In cardiovascular tissues, isoketals and isolevuglandins (isoLGs) have the highest reactivity, and thus are the most damaging. Levels of lipid peroxidation and associated protein adducts have been found to be increased in the blood and vascular cells of patients with a variety of cardiovascular-associated pathologies, and these pathologies can be prevented through treatment with isoketal scavengers, such as 2-HOBA. Notably, these scavengers are best suited as preventatives to block the formation of damage inducing adducts, as they are unable to reverse pre-existing damage.

Hypertension: Vascular oxidative stress is associated with aortic stiffening and hypertension. In a small study, hypertensive patients (n=28) were found to have higher plasma levels of F2-isoprotanes (10.7 ± 1.6 ng/ml vs. 17.7 ± 2.2 ng/ml, P < 0.05), which are formed by the peroxidation of arachidonic acid and serve as a precursor for reactive isoketals, relative to their normotensive counterparts (n=15) [20]. F2-isoprostane levels were also correlated with pulse wave velocity, a measure of aortic stiffness (Spearman r=0.44, P<0.01). In aortic biopsies from these patients, the level of isoketal protein adducts correlated with the severity of fibrosis based on collagen deposition (Spearman r=0.80, P<0.01), and with the level of inflammation based on T cell infiltration (Spearman r=0.65, P<0.05). These isoketal protein adducts are thought to be immunogenic by serving as neoantigens for antigen presenting cells. The level of isoketal adducts was found to be 3-fold higher in peripheral blood cells from hypertensive patients (n=12) relative to normotensive people (n=8) and the percentage of isoketals in antigen producing $CD14^+$ macrophages (β=1.06, p=0.02) and $CD38^+$ dendritic cells (β=1.14, p=0.03) was found to correlate with systolic blood pressure in these patients [12]. Similarly, in mouse models involving vascular oxidative stress and hypertension, there is an accumulation of damage inducing isoketals in the heart and vasculature [12; 20]. Notably, there is an increase of isoketals in antigen presenting cells, including dendritic cells, which in turn leads to the activation of inflammatory T cells. In these mouse models, early treatment with 2-HOBA protects against isoketal formation, hypertension, aortic stiffening, fibrosis, and vascular inflammation. However, late administration, after the onset of pathology, was ineffective [20].

Oxidative stress also drives the production of neutrophil extracellular traps (NETs), which have been shown to accumulate in the aorta of patients with hypertension [21]. NETosis increases in response to isolevuoglandin (isoLG) formation in neutrophils. In isolated primary human neutrophils, treatment with ionomycin, which promotes oxidative stress, led to the formation of isoLGs and induction of NETosis [21]. These effects could be prevented through the pretreatment of the neutrophils with a cell permeable form of 2-HOBA. In a mouse model of angiotensin-II-induced hypertension, neutrophil levels in the circulating blood were augmented, coupled with an increase in NETosis within the aorta [21]. Treatment with 2-HOBA during angiotensin-II administration attenuated the migration of neutrophils and formation of NETs.

Pulmonary Arterial Hypertension: Patients with PAH that carry mutations in BMPR2, a receptor kinase mutated in >70% of familial cases of PAH, have altered cellular metabolism in their pulmonary endothelial cells, and the altered fatty acid metabolism contributes to vascular pathology. These patients have higher circulating levels of glutamine for use as a carbon source for energy production [22]. In a corresponding mouse model, it was determined that this requirement for glutamine as an

energy source stems from the loss of function of the master regulator of cellular metabolism, SIRT3 [22]. The function of SIRT3 is compromised by covalent modification by reactive carbonyl species, and in the mouse model treatment with 2-HOBA prevented the formation of these SIRT3 modifications and the development of PAH. In another mouse model, in which AKR strain mice are fed a high-fat diet to induce pulmonary hypertension, mice administered 2-HOBA for the 12 or 20 weeks of induction process had attenuated increases in right ventricular systolic pressure [23]. The co-treated mice also resisted adverse metabolic changes, such that they had 60% higher right ventricular energy production and a normalization of right ventricular ceramide levels as well as the normalization of several circulating inflammatory cytokines. Similar protective effects were observed with 2-HOBA administration in the Bmpr2 mutant mouse PAH model [23].
Based on these studies, 2-HOBA will be tested in a small (n=12) unblinded Phase 2 trial in patients with WHO Functional Class II-IV PAH (NCT06176118). The primary outcome will be the change in acetylated SOD2 and LCAD in plasma.

Atherosclerosis: Oxidative modification of lipoproteins promotes atherosclerosis related vascular pathology. Oxidation can enhance the pathogenic nature of LDL, as oxidized LDL can promote foam cell formation, and induce immune cell activation and inflammation. Meanwhile, oxidative modification of HDL can inhibit its protective functions. Individuals with familial hypercholesterolemia were found to have increased levels of the reactive carbonyl species, malondialdehyde (MDA), and the formation of MDA adducts on HDL particles [24; 25]. The presence of these MDA modified HDL particles inhibits the activity of HDL-associated antioxidant enzymes, such as paraoxonase 1 (PON1), inhibits ApoA1 exchange, and reduces cholesterol efflux capacity [25]. In a mouse model of hypercholesterolemia, 2-HOBA treatment reduced atherosclerosis by 31% in proximal aortas and by 60% in en face aortas without significantly affecting blood lipid levels [24]. The protective effects stem from a reduction in macrophage cholesterol stores due to enhanced efferocytosis, and reduced inflammation. Pretreatment of macrophages from atherosclerotic Apoe-/- mice with 2-HOBA partially prevented the formation of MDA-HDL adducts in response to the pro-oxidant myeloperoxidase, and reduced induction of the pro-inflammatory cytokines, IL-1β and IL-6 [25]. Similarly, in the Ldlr-/- mouse model, pretreatment of mice with 2-HOBA (1 g/L in drinking water) prior to (two weeks) and during (16 weeks) the induction of atherosclerosis via a high fat diet, attenuated ApoA1 oxidation and MDA-HDL adduct formation [25]. This mitigated deficits in HDL function, such that the HDL particles of treated mice had 37.5% higher cholesterol efflux capacity, and 18.5% higher PON1 activity.
Overall, 2-HOBA treatment protected against the formation of reactive carbonyl species adducts of HDL, thereby preserving its protective functions.

Based on the elevated presence of oxidatively modified HDL particles in patients with familial hypercholesterolemia and the protective effects of 2-HOBA in reducing levels of HDL modification in preclinical models, 2-HOBA is currently being tested for its ability to reduce HDL modification and improve HDL function in patients with familial hypercholesterolemia in a Phase 2 trial (NCT04941599).

Atrial fibrillation: Inflammation and oxidative stress are implicated in the development of atrial fibrillation. Thus, compounds which act on these processes, such as 2-HOBA, may have a protective role. Reactive carbonyls have been implicated in the development of atrial fibrillation stemming from deficiency of lymphocyte adaptor protein (LNK) [26]. Certain SNPs, such as rs3184504, are associated with reduced LNK function and increased risk for cardiovascular disease [27]. Mice deficient in LNK show elevated levels of systemic inflammation and oxidative stress as well as an increased propensity toward developing atrial fibrillation [26]. These mice also show an accumulation of reactive carbonyl adducts in the atria [27]. Of note, Lnk-/- mice do not necessarily also exhibit atrial fibrosis and cardiomyocyte calcium mishandling, which are common drivers of atrial fibrillation, therefore it is unclear how much this mechanism contributes to atrial fibrillation more broadly [26]. Treatment of Lnk-/- mice with 2-HOBA for three months partially normalized electrophysiological parameters in the atrial cells, including prolonged action potential duration, late Na+ currents, and transient outward K+ currents [27]. 2-HOBA was also associated with improved mitochondrial function, but did not significantly impact atrial immune cell infiltration.

The accumulation of preamyloid oligomers in the atrial wall can disrupt electrical activity and has been associated with atrial fibrillation [28]. Hypertension is the most prominent cardiovascular risk factor associated with atrial fibrillation. The burden of preamyolid oligomers has been shown to be elevated in atrial tissue from patients with hypertension [29]. Similarly, atrial levels of preamyloid oligomers and isoLG adducts were elevated even at early timepoints in a mouse model of angiotensin-II-induced hypertension [28]. Pretreatment with 2-HOBA (1 g/L in drinking water) starting three days prior to the angiotensin-II infusion, attenuated the formation of atrial preamyloid oligomers, isoLG adducts, and largely prevented the induction of hypertension-associated atrial fibrillation in the mice.

In a cell culture model of atrial fibrillation, the generation of reactive γ-ketoaldehyde adducts promoted the production of preamyloid oligomer cytotoxic species, and induced a stress response. 2-HOBA treatment prevented these deleterious effects [30]. Exposure of cultured atrial cells to isoLGs induces oxidative mitochondrial damage that alters mitochondrial function, respiratory capacity, and cell electrophysiology, including Ca^{2+}, Na+, and K+ currents, in a manner that increases the propensity for arrhythmia [31]. Pretreatment with 2-HOBA protects against these metabolic and electrophysiological

changes by reducing the formation of isoLG adducts and the associated generation of mitochondrial ROS.

These studies suggest that the formation of reactive carbonyl species and associated adducts occurs early in the development of atrial pathology, and that early intervention with scavengers can mitigate the damage incurred by these reactive species. It is currently unclear how effective they would be when administered starting at later stages in the context of structural and functional abnormalities, or for preventing the reoccurrence of arrhythmia events.

Based on the ability of 2-HOBA to reduce the propensity for atrial fibrillation in preclinical models, it was tested in a pilot randomized, double-blind, placebo-controlled, Phase 2 clinical trial in participants undergoing cryo- or radiofrequency catheter ablation for atrial fibrillation (NCT04433091). The trial was designed to include 162 participants who would receive placebo or 2-HOBA (750 mg TID) for seven days prior to ablation and for 28 days post-ablation [32]. Participants received smartwatches with the capacity to detect and record atrial arrhythmias. The primary endpoint of the trial was an episode of atrial fibrillation, atrial tachycardia, or atrial flutter lasting 30 seconds or more within 28 days post-ablation. However, due to complications stemming from conducting the trial during the Covid-19 pandemic, the trial was terminated early, including only 89 participants, with some outcome measures including only half of participants due to the inability to perform scheduled blood draws. Thus, the trial was not adequately powered for its study outcomes. Numerically, a higher number of participants in the 2-HOBA group experienced smartwatch detected atrial fibrillation events (26/43 vs 14/39) at interim analysis, leading to the termination of the trial for futility. Overall, this study highlights the importance of early intervention, ideally prior to an oxidative stress-inducing event, and that determining a dosing strategy that effectively lowers isoLG adduct formation will be critical for determining the therapeutic efficacy of 2-HOBA in future trials.

Heart Failure: In a mouse model of heart failure (transverse aortic constriction), the level of isoLG protein adducts was increased in the heart and lung [33]. Treatment with 2-HOBA reduced the formation of these deleterious adducts, cardiac hypertrophy, lung fibrosis, and the infiltration of pro-inflammatory macrophages and leukocytes. The isoLG-modified proteins can serve as neoantigens that activate CD4+ T cell receptors (TCR). The absence of CD4 antigen presentation and CD4+ T cells prevented the induction of cardiac dysfunction in response to transverse aortic constriction in mice, while mice with CD4+ T cells but lacking cognate antigen presentation were partially protected, suggesting a role for immune cell activation toward cardiac antigens [34]. Cardiac dysfunction was attenuated, based on the preservation of fractional shortening, dP/dt max, and dP/dt min in mice treated with 2-HOBA (1g/L in drinking water) for four weeks following the aortic constriction surgery.

Notably, an accumulation of isoLG protein adducts was observed in the left ventricles of patients with end-stage heart failure, suggesting that this mechanism is relevant in humans [34]. 2-HOBA also attenuated post-myocardial infarction-induced adverse cardiac remodeling in the mouse model of anterior descending artery ligation-induced myocardial infarction [35]. Treatment with 2-HOBA (1 g/L in the drinking water) starting after the ligation reduced levels of isoLG protein adducts in the cardiac tissue of the mice, and suppressed the induction of oxidative stress markers, such as MDA. 2-HOBA treatment was also associated with a reduction in the level of cardiac apoptosis and levels of the pro-inflammatory cytokines, IL-1β, TNF-α, and MCP-1.

Gastrointestinal cancers: POTENTIAL RISK REDUCTION (Preclinical)
Oxidative stress damage has been identified as a contributing factor to the development of gastrointestinal cancers.
Gastric cancer: The presence of the bacterial gastric pathogen associated with gastric ulcers, *Helicobacter pylori*, also increases the risk for gastric cancer, due to its induction of inflammation and DNA damage in gastric tissue [36]. In transgenic FVB/N insulin-gastrin mice infected with *H. pylori* (cagA+ strain), treatment of 2-HOBA (1 or 3 mg/mL) in the drinking water starting seven days after infection attenuated mucosal hyperplasia and the infiltration of immune cells into gastric tissue [36]. Gastric levels of 2-HOBA were inversely associated with the degree of tissue dysplasia and carcinoma. Expression of pro-inflammatory cytokines, including IL-1β, TNF-α, Th17, and IFN-γ, were also reduced in response to 2-HOBA. Levels of DNA damage, including the formation of acrolein adducts, were also attenuated by treatment with 2-HOBA in FVB/N insulin-gastrin mice [37].

Colorectal cancer: High levels of isoLG adducts have been observed in the colonic epithelial cells of patients with colorectal cancer [38]. 2-HOBA was found to be active within colonic tissue following administration through the drinking water in mice [38]. Treatment with 2-HOBA slowed the growth of tumors and reduced tumor burden in several colorectal cancer mouse models, including a xenograft model with HCT116 cells, and a Cre-inducible sporadic model (CDX2P-CreERT2;Apcfl/fl) [38]. A reduction in tumor size with 2-HOBA was also observed in the inflammatory colitis-induced azoxymethane and dextran sulfate sodium model.

***Esophageal cancer*:** Individuals with gastroesophageal reflux disease (GERD) are at a higher risk for esophageal cancer, which may be related to increased levels of reactive carbonyl species and associated protein adducts. Patients with GERD were found to have a trend toward higher levels of isoLG in their esophagus, while levels were largely undetectable in healthy controls [39]. The esophageal tissue from

GERD patients also showed evidence of misfolded p53 aggregates [40]. IsoLG protein adducts also accumulated in the esophagus of a GERD mouse model, and in esophageal cells exposed to GERD-like conditions. The tumor suppressor p53 was one of the proteins adversely affected by the presence of reactive isoLGs, and its loss of solubility/function may drive cancer risk. Treating esophageal cells with 2-HOBA prevented the formation of isoLGs, and preserved the function of p53 [39; 40]. Similarly, treatment of mice with 2-HOBA (8 mM in drinking water) for ten days starting two weeks after GERD-inducing esophagojejunostomy surgery mitigated the formation of misfolded p53 aggregates [40].

Autoimmune disease: POTENTIAL BENEFIT WITH EARLY TREATMENT (Preclinical)
Evidence from patients and preclinical models suggests that modification of native proteins by reactive aldehydes may contribute to the formation of autoantigens that activate deleterious immune responses toward host tissue. As such, early intervention with scavengers, like 2-HOBA, may help dampen inflammatory activity and preserve tissue integrity/function.
Lupus: Systemic lupus erythematosus is an autoimmune condition involving inappropriate immune responses toward autoantigens, and is often accompanied by hypertension [41]. IsoLG-modified proteins may serve as autoantigens and play a role in the etiology of lupus. Levels of oxidative stress were found to be markedly elevated in the monocytes of patients with lupus, including a nine-fold increase in levels of superoxide and an eight-fold increase in isoLG adducts [41]. That these isoLG adducts may serve as autoantigens is suggested by the positive correlation between levels of reactivity to isoLG adducts using iso-LG antibodies with disease severity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (n=29; R^2=0.16). In the B6.SLE123 mouse model, levels of isoLG adducts were found to be elevated in immune cell subsets with antigen presenting capacity, such as dendritic cells, and B cells, prior to the onset of symptoms, suggesting the formation of isoLGs may play an early role in disease processes [41]. Treatment of these mice starting at this early time point (7 weeks of age) with 2-HOBA (1 g/L in drinking water) attenuated the accumulation of isoLG adducts in a variety of myeloid and lymphoid cell subsets. This was accompanied by the mitigation of disease-related phenotypes and pathology, including the development of hypertension, immune cell infiltration into the kidney, renal inflammation and dysfunction. Additionally, early treatment with 2-HOBA was associated with decreased production of autoantibodies. A similar early accumulation of isoLG adducts was observed in the NZBWF1 mouse model, which also experienced a reduction in autoantibodies and protection against renal dysfunction in response to 2-HOBA treatment.

Rheumatoid arthritis: 2-HOBA is currently being tested in a randomized, placebo-controlled, double-blind Phase 2 clinical trial at a dose of 750 mg TID for four weeks in patients with rheumatoid arthritis

(estimated n=32) (NCT05274243). The primary outcomes are safety/tolerability and the change in percentage of cellular isoLG adducts between active and placebo arms.

Safety: It has been well-tolerated with no evidence of drug-related adverse events in Phase 1 trials in healthy adults and in animals treated for several months. The effects of chronic use in humans still need to be characterized.

Types of evidence:

- 3 Phase 1 clinical trials for safety and PK in healthy volunteers (n=18; n=18; n=18)
- Several laboratory studies

2-HOBA acetate has been shown to be safe and **well-tolerated in Phase 1 trials.** All adverse events were mild and not expected to be drug related in a small open-label single ascending dose (SAD) clinical trial in healthy volunteers (n=18, age 27.2 ±5 years) (NCT03176940) [42]. Participants showed no clinically meaningful changes in vital signs, ECG measures, or clinical laboratory parameters. Orally administered 2-HOBA was rapidly absorbed with an average T_{max} of 1.6 hours, and the C_{max} increased proportionally with dose. A placebo-controlled multiple ascending dose (MAD) study was conducted in 18 adults under age 60, assessing doses of 500 mg TID and 750 mg TID (administered as 250 mg capsules) for 14 days (NCT03555682) [43]. 2-HOBA was generally well tolerated. Adverse events were mild and transient. Headache (6 participants) was the most commonly reported adverse event. There were no dose-dependent adverse events, and adverse events were not classified as drug related. There were no clinically significant changes in ECG recordings, vital signs, or laboratory parameters. The accumulation of 2-HOBA in the multiple dosing study was higher (1.19–1.94) than predicted (1.06–1.22), likely due to a longer effective half-life (~4-5 hours). In contrast to the SAD study, the two doses did not show dose-proportional systemic exposure, but instead, exposure levels were similar for the two doses, which may have been related to high inter-subject variability. This suggests that additional factors may influence the bioavailability of 2-HOBA *in vivo*.
Salicylic acid is the major metabolite of 2-HOBA. It has anti-inflammatory properties and is also the major metabolite of aspirin (acetylsalicylic acid) [43]. However, the levels of salicylic acid (12.8 ± 3.7 mg/L) following administration of the highest tested dose (750 mg TID) were found to be well below the therapeutic range (150–300 mg/L), and there was no evidence of cyclooxygenase inhibition in response to 2-HOBA administration [43].

Another Phase 1 MAD trial conducted in 18 older adults (aged 55 and 79 years) also tested 2-HOBA at doses of 500 mg TID and 750 mg TID for 14 days (NCT03556319). The trial was completed in 2021. 2-HOBA was reported to be safe in this population, but study results have not yet been made available.

2-HOBA acetate was also tested for toxicity in rabbits, rats, mice, and human cells in preclinical studies. All toxicology studies, including the human study, were done using a formulation of 2-HOBA manufactured by TSI, China (Lot# 16120312). The no-observed-adverse-effect level (NOAEL) was found to be 1000 mg/kg bw/day in rodents [44; 45] and rabbits [46], which translates to a human equivalent dose of approximately 10 g per day (for a 75 kg man). Mice treated orally with 10 g/L 2-HOBA showed signs of toxicity, including weight loss and hunching behavior [47]. 2-HOBA was well-tolerated in animals following subchronic administration for 90 days, and was not associated with any biologically meaningful changes in body weight, histopathology, biochemical or hematological parameters [44; 46]. Based on *in vitro* studies in human cells, it is not cytotoxic or mutagenic, does not induce CYP enzymes, and has low risk for cardiac QT wave prolongation [48].

Reactive carbonyl species scavengers are anticipated to be safer and more effective than ROS scavengers, as endogenous ROS play important cellular functions [1]. The biological roles of reactive carbonyl species are not well characterized, but similar to ROS, there is some evidence that they also impact cellular signaling, though to a lesser degree. Therefore, at high levels, the scavengers could potentially interfere with some cellular functions. Reactive carbonyl species play a role in activating the endogenous Nrf2 antioxidant pathway, however, since this activation involves thiol reactivity, it is unlikely to be significantly impacted by amine-based scavengers, such as 2-HOBA.

2-HOBA has been shown to have modest immunomodulatory properties *in vivo* [18]. Although there has not been any evidence of immunosuppression in the studies conducted thus far, reactive carbonyl species are used by neutrophils and macrophages in host defense against pathogens [16]. Therefore, high levels of reactive carbonyl scavengers, such as 2-HOBA, could potentially impact immune function and the ability to fight infections.

Sources and dosing:

2-HOBA is available OTC as dietary supplement and is being developed as a pharmaceutical agent in a 2-HOBA acetate oral capsule formulation. Due to its short half-life, current formulations of 2-HOBA need to be administered every eight hours (i.e. TID dosing) to maintain physiologically active levels. In a Phase

1 SAD trial, the maximum tested dose was an 825 mg oral gel capsule of 2-HOBA acetate, which corresponds to 560 mg of 2-HOBA. In multiple dosing trials, 2-HOBA has most commonly been dosed at 750 mg TID. Hobamine is the patented formulation of 2-HOBA from TSI Health Sciences.

Research underway:

All of the clinical trials conducted and currently planned for 2-HOBA thus far have been sponsored by Metabolic Technologies Inc/MTI Biotech Inc, and/or Vanderbilt University.
There are currently two active clinical trials and two registered/planned Phase 2 clinical trials testing 2-HOBA.

A randomized, placebo-controlled, double-blind Phase 2 clinical trial is testing 2-HOBA (750 mg TID for six weeks) in patients with familial hypercholesterolemia (estimated n=72) (NCT04941599). The primary outcome is the change in HDL cholesterol efflux capacity based on a macrophage cholesterol efflux assay. The study has an expected completion date in late 2025.

A randomized, placebo-controlled, double-blind Phase 2 clinical trial is testing 2-HOBA (750 mg TID for four weeks) in patients with rheumatoid arthritis (estimated n=32) (NCT05274243). The primary outcomes are safety/tolerability and the change in percentage of cellular isoLG adducts between active and placebo arms. The trial has an expected completion date in 2025.

There is a planned randomized, placebo-controlled, double-blind, dose-finding Phase 1b/2a trial testing 2-HOBA (250, 500, or 750 mg TID for 16 weeks) in patients with MCI/early AD (estimated n=48) (NCT06432166). The primary outcomes are safety/tolerability and the change in CSF levels of the dilysyl-malondialdehyde crosslink and the lysyl-levuglandin adduct of CSF proteins in a dose-responsive relationship.

There is a planned Phase 2 open-label trial testing 2-HOBA (TID) for 12 weeks in patients with pulmonary arterial hypertension (WHO Functional Class II-IV) (estimated n=12) (NCT06176118). The primary outcome is the change in acetylated SOD2 and LCAD in plasma.

Search terms:
Pubmed, Google: 2-Hydroxybenzylamine or 2-HOBA or 2-aminomethylphenol or salicylamine +

- Alzheimer's disease, neurodegeneration, reactive carbonyl species, isoketals, cardiovascular, diabetes, aging, lifespan, safety, clinical trials

Websites visited for 2-HOBA:

- Clinicaltrials.gov
- DrugAge
- PubChem
- DrugBank.ca

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