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.

Berberine

Evidence Summary

Many clinical studies suggest berberine may effectively manage diabetes, dyslipidemia, and hypertension, but no studies have tested whether it can prevent or treat cognitive decline.

Neuroprotective Benefit: Preclinical evidence suggests berberine may protect neurons by inhibiting beta-secretase and reducing inflammation, but it may also promote neurodegeneration when insult/damage is already present. No clinical trials have tested whether it can prevent dementia.

Aging, mortality and related-health concerns: Berberine is effective in managing age-related conditions that contribute to mortality, including diabetes, high cholesterol and hypertension. Larger and longer, well-controlled clinical trials are needed to confirm these findings.

Safety: Berberine is likely safe for short-term consumption, but evidence is lacking for chronic safety. Because of its demonstrated inhibition of multiple liver enzymes involved in metabolism of common drugs, caution should be taken before adding berberine to any medication regimen.

What is it? Berberine is an alkaloid found in many species of the plant genus *Berberis*, as well as shrubs and trees of the poppy and cork families. It can be isolated from roots, rhizomes, stems and bark. Berberine is also the major alkaloid component of Goldenseal (*Hydrastis canadensis*), an herb commercially marketed to promote immune health.

Modern science has identified berberine as a multi-functional chemical with many potential *in vivo* targets. Clinical studies indicate efficacy for type 2 diabetes and cholesterol while laboratory studies suggest possible efficacy against cancer and dementia (see below for details).
Berberine is commercially available as a dietary supplement from a variety of sources.

Neuroprotective Benefit: Preclinical evidence suggests berberine may protect neurons by inhibiting beta-secretase and reducing inflammation, but it may also promote neurodegeneration when insult/damage is already present. No clinical trials have tested whether it can prevent dementia.

Types of evidence:

- No clinical trials or observational studies
- Numerous animal model studies
- Numerous *in vitro* cellular studies

There is no clinical evidence that berberine is neuroprotective in humans or prevents or treats cognitive decline, Alzheimer's disease (AD) or related dementias. However, preclinical studies point to several potential mechanisms of action relevant to Alzheimer's disease. Additionally, as discussed in the next section, berberine can help to manage type 2 diabetes and high cholesterol, both contributing factors of accelerated aging and AD. Although several groups have suggested berberine should be explored for use in patients with AD, there are currently no planned or ongoing clinical trials.

Preclinical studies in mouse, rat and rabbit AD models suggest that berberine benefits several aspects of disease pathology including inhibiting beta-secretase (Panahi et al, 2013), reducing beta-amyloid production and plaque burden (Panahi et al, 2013), reducing tau hyperphosphorylation via GSK-3β inhibition (Durairajan et al, 2012), reducing neuroinflammation (Durairajan et al, 2012) and improving cognitive function including learning and spatial memory (Zhu et al, 2006; Durairajan et al, 2012). Several *in vitro* studies also demonstrate similar effects on neuronal cells and other cell types (Asai et al, 2007; Zhu et al, 2011), including berberine's inhibition of acetylcholinesterase activity (Bonesi et al, 2013) as well as suppression of microglial inflammation (Lu et al, 2010; Jai et al, 2012). Several groups have synthesized berberine derivatives and chemical conjugates that show anti-acetylcholinesterase

activity *in vitro* (Shan et al, 2011; Jiang et al, 2011; Su et al, 2013). Importantly, though, none of these activities have been demonstrated yet in humans.

In a rat model of Alzheimer's (Aβ42 injected into the prefrontal cortex), berberine partially restored memory impairment and firing frequency of hippocampal (CA1) neurons (Haghani et al., 2015).

In a mouse model of postoperative cognitive dysfunction, where aged mice received abdominal surgery under isoflurane anesthesia, berberine administration (10 mg/kg, i.p.; 3 injections post-op) attenuated cognitive impairment, decreased markers of inflammation (IL-1β, IL-6) in the hippocampus and prefrontal cortex, and decreased the number of activated microglial cells (IBA1-positive) (Zhang et al., 2016). Berberine may protect from postoperative cognitive dysfunction by suppressing neuroinflammation in aged mice.

In contrast, some studies suggest that berberine treatment may promote apoptosis when initiated after insult/damage. In rodent and cell culture models of hypoxia, berberine promoted cell survival if given before the injury but promoted cell death if given after the injury (Zhang et al., 2012). Berberine appears to regulate neuronal apoptosis in cerebral ischemia but the direction of change may depend on the degree of cellular injury, where it may cause greater harm if initiated after the injury. Similarly, in rodent and cell culture models of Parkinson's disease, berberine treatment increased the lesion-induced toxicity and death of dopamine neurons in the substantia nigra (Kwon et al., 2010).

Thus, in the presence of damage, berberine may accelerate neurodegeneration. These opposing effects may be due, in part, to berberine's inhibitory effect on mitochondrial complex I of the electron transport chain (Turner et al., 2008)(discussed below). While inhibition of complex I has been identified as a potential target for lifespan extension in transcriptome analyses (Baumgart et al., 2016) and studies with CP2 (delayed reproductive senescence) (Zhang et al., 2015), stressing the electron transport chain (hormesis) may be harmful when neurodegeneration is already in progress. If these preclinical findings translate to the clinic, then berberine may be harmful in people with dementia and possibly in people experiencing cognitive decline, as neurodegeneration precedes cognitive symptoms.

APOE4 interactions: No evidence exists yet to suggest different effects of berberine in *APOE4* carriers versus non-carriers.

Aging, mortality and related health concerns: Berberine is effective in managing age-related conditions that contribute to mortality, including diabetes, high cholesterol and hypertension. Larger and longer, well-controlled clinical trials are needed to confirm these findings.

Types of evidence:

- 2 meta-analysis covering 28 clinical trials (overlap of 4 trials) of diabetes
- 2 meta-analysis covering 17 clinical trials (overlap of 2 trials) of dyslipidemia
- 1 meta-analysis covering 4 clinical trials of hypertension
- 5 clinical trials using berberine as part of a combination therapy for dyslipidemia
- 1 clinical trials in women with polycystic ovary syndrome
- Numerous animal model studies demonstrating mechanisms of action

Although there is no evidence on berberine and lifespan or mortality risk, multiple clinical trials have demonstrated its effectiveness in managing type 2 diabetes, dyslipidemia and hypertension as well as treating metabolic aspects of polycystic ovary syndrome in post-menopausal women and inflammation associated with acute coronary syndrome.

Diabetes: Two meta-analyses comprising 28 trials (4 trials overlap between the two analyses) and nearly 3,000 patients suggest berberine helps to manage type 2 diabetes and offers improved control of blood glucose when combined with other treatments (e.g., metformin, TZDs or GLP1 agonists) (Dong et al, 2013; Lan et al, 2015). The trials averaged 3 months in duration and included berberine doses ranging from 0.2-0.5 g, 3 times daily. No serious adverse events were reported but some gastrointestinal (GI) disturbances were observed. All of these trials, however, were small (usually less than 100 subjects), short in duration, and varied in methodological rigor. A longer, larger, well-controlled study would help to confirm these reported findings. None of these studies suggest that berberine can prevent diabetes. Despite the popularity of supplements such as berberine in people with diabetes, there are no clinical guidelines from expert groups. The burden falls on clinicians to become familiar with these products so they can provide the evidence on efficacy and safety to their patients (Shane-McWhorter, 2013).

Berberine may regulate blood glucose by inhibiting dipeptidyl peptidase IV (DPP-4), although this mechanism has only been shown *in vitro* (Al-masri et al, 2009). Inhibition of DPP-4 increases levels of incretins (GLP-1 and GIP), which inhibits glucagon release and increases insulin levels.

In vitro studies have shown that berberine and dihydroberberine, a derivative of berberine with higher bioavailability, inhibit mitochondrial complex I of the electron transport chain and activate AMPK (Turner et al., 2008). Inhibition of complex I and/or an increase in AMPK activity may promote insulin sensitivity and is relevant for treatment of type 2 diabetes. Complex I and AMPK are also targets implicated in anti-aging pathways and lifespan extension through caloric restriction (Vaiserman et al., 2016).

Dyslipidemia: Two meta-analyses comprising 17 trials (2 trials overlap between the two analyses) and over 1,300 patients suggest berberine effectively manages dyslipidemia (Dong et al, 2013; Lan et al, 2015). Berberine was as effective as statins at lowering total cholesterol and LDL and even better when combined with a statin. Interestingly, berberine either alone or combined with a statin also effectively lowered triglycerides and raised HDL. While some GI side effects were observed, no serious adverse events were reported. As with the diabetes trials, these trials were short (usually 3 months), small (usually less than 100 people) and of varying quality. A larger and longer trial is needed to confirm these findings.

Several other small clinical trials have evaluated berberine (500 mg, 3 times daily) as part of a combination therapy, most commonly along with policosanol (a mix of long-chain plant alcohols available as a dietary supplement) and red yeast rice (Cicero et al, 2007; Affuso et al, 2010; Marazzi et al, 2011; Cianci et al, 2012; Pisciotta et al, 2012). All of these trials yielded similar findings to the trials that used berberine alone or in combination with a statin; however, in the trial that examined the combination therapy versus berberine alone, greater reductions in total cholesterol and triglycerides were noted (Cicero et al, 2007). Compared to metformin in a small trial of post-menopausal women with polycystic ovary syndrome, berberine treatment more effectively lowered total cholesterol, triglycerides and LDL while raising HDL (Wei et al, 2012).

These clinical trial findings, as well as the findings of the diabetes trials, are supported by numerous *in vitro* and animal model studies suggesting berberine inhibits Complex 1 of the mitochondrial respiration machinery (Turner et al, 2008; Zhao et al, 2013; Xu et al, 2014), activates AMPK (Turner et al, 2008; Gomes et al, 2012; Xu et al, 2014; Zhao et al, 2013; Zhao et al, 2014; Zhang et al, 2014) and increases liver expression of the LDL receptor (Kong et al, 2004).

Hypertension: One meta-analysis comprising 4 clinical trials and ~600 patients suggests berberine is as effective as amlodipine and metoprolol at managing high blood pressure and when added to these drugs can achieve more effective hypertension management than with the drugs alone (Lan et al, 2015).

However, the 4 included trials were all small and short (only 1-2 months), so a longer, larger trial is needed to validate these findings. Several preclinical studies suggest berberine improves markers of endothelial cell function (Wang et al, 2009; Cheng et al, 2013).

Aging biology: While no published studies examined lifespan extension with berberine treatment, one *in vitro* study suggests berberine prevents the transition from cell cycle arrest to cell senescence (Zhao et al, 2013). How this finding relates to organismal aging remains unknown. Additionally, as noted above, several of berberine's actions are linked in the aging literature to lifespan extension, including inhibition of mitochondrial Complex 1 and activation of AMPK (Zhang et al., 2015; Vaiserman et al., 2016). It should also be noted, however, that *in vitro* studies have shown that berberine causes DNA damage (Chen et al, 2013), which is a proposed mechanism of biological aging.

Safety: Berberine is likely safe for short-term consumption, but evidence is lacking for chronic safety. Because of its demonstrated inhibition of multiple liver enzymes involved in metabolism of common drugs, caution should be taken before adding berberine to any medication regimen.

Types of evidence:

- 4 meta-analysis
- 1 clinical trial
- Numerous preclinical studies

Although berberine is widely regarded as safe for consumption, the trials testing it for diabetes, high cholesterol and hypertension have been 3 months or shorter. No epidemiology has looked at long-term use. Little information is available about its safety for chronic use.

In the meta-analysis discussed above, adverse events (mostly GI) ranged from 5 to 15% and were dose-dependent, with the highest percentage reported for doses over 1 g/day (Dong et al, 2013; Lan et al, 2015).

In a 2015 meta-analysis of 27 randomized controlled trials (RCTs) in patients with type 2 diabetes, hyperlipidemia, or hypertension (total of 2,569 patients), no serious adverse events were reported with berberine treatment (Lan et al., 2015). Minor side effects included nausea, diarrhea, constipation, abdominal distension, and abdominal pain. All side effects were tolerable without having to discontinue treatment. However, the quality of included studies was suboptimal and the trials were

generally short in duration (the longest trial was 120 days). Larger, longer, placebo-controlled trials using standardized preparations will better define the roles of berberine.

Two other meta-analyses, one in people with high cholesterol that included 11 RCTs and 1,300 people (Dong et al., 2013) and the other in people with type 2 diabetes that included 14 RCTs with 1,068 people (Dong et al., 2012) also reported that side effects were mild and tolerable (mostly minor gastrointestinal effects as described above) and no significant differences in the incidence of adverse events were found between berberine and control groups.

However, a 2012 clinical trial of 17 healthy male adults demonstrated that 300 mg, 3 times daily consumption of berberine for 2 weeks inhibits a number of liver enzymes involved in drug metabolism, including the metabolism of the benzodiazepine midazolam, the cough medicine ingredient dextromethorphan and the angiotensin 2 receptor blocker losartan (Guo et al, 2012). Caution should be taken when combining prescription medications and berberine and berberine-containing products.

Several recent studies cast doubt on berberine's general safety. A 2-year toxicology study by the National Toxicology Program dosing rats with Goldenseal (at doses containing a human equivalent dose of only 60 mg daily of berberine) reported significantly increased tumor incidence (Dunnick et al, 2011). Toxicity was due to berberine's inhibition of topoisomerase I and II, two enzymes critical in repairing DNA damage and that the DNA damage was caused by berberine (Chen et al, 2013). It remains uncertain how these findings translate to humans.

Several other preclinical studies suggest berberine may be neurotoxic (Kysenius et al, 2014) or exacerbate Parkinson's disease pathology (Shin et al, 2013). Because of berberine's potential to accumulate in the CNS (Kysenius et al, 2014), these reports warrant further study.

Sources and dosing: Berberine is commercially available from a variety of sources. Berberine can be purchased as a dietary supplement in doses ranging from 100-1000mg. Typical doses used in clinical trials range from 0.3g-1.5g daily. Berberine is also a component of Goldenseal (nearly 4% by weight) (Dunnick et al, 2011), which is also commercially available as an oil or gel capsule. While 22% of diabetes patients use herbal products and 67% use some type of vitamin or supplement, there are no clinical guidelines from expert groups or organizations for these products, including for berberine (Shane-McWhorter, 2013). Despite the number of clinical studies reporting benefit in diabetes patients, longer-term, higher quality studies are likely critical before official recommendations can be made in this patient population.

Additionally, berberine's therapeutic effectiveness for some conditions may be limited by observations that it is poorly bioavailable (Ye et al, 2009), only reaches low nanomolar plasma concentrations in humans and animals after ingestion (Ye et al, 2009) and, at least in rodent models, can accumulate in lungs, liver and brain, eventually reaching low micromolar concentrations (Durairajan et al, 2012).

Despite its apparent poor bioavailability, therapeutic levels are achievable for diabetes, cholesterol and hypertension management. *In vitro* studies have shown that dihydroberberine, a derivative of berberine, has higher bioavailability (Turner et al., 2008) and may be a more promising compound for therapy. Additionally, berberine was shown in rodent studies to accumulate in the CNS (Kysenius et al, 2014), which may have implications for its potential as a treatment for CNS diseases.

Women who are pregnant or breastfeeding should not take berberine, as it may cross the placental barrier and pass into breast milk (Kumar et al., 2015).

More information on safety, doses, and drug interactions can be found on medlineplus.gov.

Research underway: While several trials are ongoing to examine berberine in the management of diabetes, high cholesterol and hypertension, there are no planned or ongoing trials as a prevention or treatment for neurodegenerative diseases, cognition, dementia, or aging biology.

Berberine has low bioavailability when taken orally, because it is poorly absorbed and its concentration is greatly reduced in the intestine before reaching the systemic circulation (intestinal first pass effect) (Liu et al., 2016). Poor absorption is partly due to self-aggregation, poor permeability, and P-glycoprotein-mediated efflux. One promising avenue of research may be to explore derivatives of berberine, such as dihydroberberine (Turner et al., 2008), which has been reported to have higher bioavailability. No clinical trials have tested this derivative yet. Other strategies to improve oral bioavailability of berberine include permeation enhancers (e.g., sodium caprate, chitosan), P-glycoprotein inhibitors (e.g., TPGS, silymarin, Tet), and lipid microparticle delivery systems (lipid microparticle drug delivery systems, self-microemulsifying drug delivery system, anhydrous reverse micelle delivery system) (Liu et al., 2016). In clinical practice, long-term safety is based on little or no absorption of berberine. Safety and dosages will need to be redefined when these approaches successfully enhance absorption in humans. Altering the epithelial transport properties of the intestine may cause problems in people, including an impaired ability of the gut immune system to recognize toxins from nutrients.

PubMed Search terms:

Berberine + following terms with and without filters for "clinical trial", "meta-analysis", and "review"

- Alzheimer's disease
- Neurodegeneration
- Dementia
- Cognition
- Cognitive decline
- Aging
- Longevity
- Lifespan
- Telomere
- Telomerase
- Diabetes
- Lipids
- Cholesterol
- Hypertension
- Blood Pressue
- Toxicology
- Safety

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.