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.

Triphala

Evidence Summary

Ayurvedic medicine used for over 1,000 years; benefits people with gingivitis, diabetes, and obesity, with preclinical studies suggesting lifespan extension and protection against numerous age-related diseases.

Neuroprotective Benefit: Triphala's antioxidant and anti-inflammatory effects appear promising but no cognitive studies have been carried out in humans or animal models.

Aging and related health concerns: Benefit has been observed in patients with diabetes, obesity, and gingivitis; numerous preclinical studies suggest benefit for lifespan extension, cancer prevention/treatment, arthritis, cataract, and hypercholesteremia.

Safety: Most clinical trials have used a mouthwash formulation of triphala for oral care; *in vitro* studies suggest that triphala mildly inhibits cytochrome P450 that metabolizes drugs and toxins.

Availability: OTC	**Dose**: 1 g/day, though higher doses (e.g., 5 g/day) have been used in diabetics	**Chemical formula:** $C_7H_6O_5$ (gallic acid); $C_{15}H_{10}O_7$ (quercetin); $C_{41}H_{32}O_{27}$ (chebulinic acid)
Half life: 1-2 hrs (gallic acid)	**BBB**: gallic acid and quercetin are penetrant	**MW**: 170.12 (gallic acid); 302.2 (quercetin); 956.67 (chebulinic acid)
Clinical trials: largest clinical trial tested triphala mouthwash in 120 people with periodontal diseases; oral ingestion of triphala was tested in 60 diabetics	**Observational studies**: none other than anecdotal records	

What is it? Triphala has been used in traditional Ayurvedic medicine for over 1,000 years. It is a polyherbal medicine consisting of dried fruits from 3 plant species: *Emblica officinalis* (Amalaki), *Terminalia bellerica* (Bibhitaki), and *Terminalia chebula* (Haritaki). Triphala is most well-known for promoting gastrointestinal health, including efficient digestion, absorption, elimination, and rejuvenation [1]. It is used as a colon cleanser, digestive, diuretic, and laxative [2]. It is also thought to promote longevity and rejuvenation in patients of all ages [1]. Research with triphala have shown that it may have antioxidant, anti-inflammatory, immunomodulatory, antibacterial, antimutagenic, hypoglycemic, and antineoplastic effects while preventing gingivitis and dental cavities.

Each of the 3 fruits contain different bioactive compounds and are thought to have different properties. For example, Amalaki, which is also known as Indian gooseberry, contains vitamin C, phenols, tannins, and other compounds and is thought to have anti-cancer properties (Healthline.com). Bibhitaki contains tannins, ellagic acid, gallic acid, lignans, and flavones and is thought to have anti-inflammatory and anti-diabetic properties. Haritaki contains terpenes, polyphenols, anthocyanins, and flavonoids and is thought to have anti-inflammatory and antioxidant properties while improving digestive issues like constipation.

As described above, there are many bioactive substances in triphala, but the major ones are thought to be gallic acid, tannins, chebulinic acid, and ellagic acid, which have antioxidant properties [1]. Other bioactive compounds include quercetin, luteolin, saponins, amino acids, etc. Triphala-derived polyphenols such as chebulinic acid are transformed by the human microbiota into bioactive metabolites, such as urolithins.

Neuroprotective Benefit: Triphala's antioxidant and anti-inflammatory effects appear promising but no cognitive studies have been carried out in humans or animal models.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- A few laboratory studies but none that specifically tested cognitive functions

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

Triphala is one of the many herbal medicine recommended by Dale Bredesen's ReCODE protocol, though no studies have examined the cognitive benefits of triphala.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Research with triphala have shown that it may have antioxidant, anti-inflammatory, and immunomodulatory effects [1], though no studies have directly tested triphala effects on cognitive functions in humans or laboratory animals.

APOE4 interactions: Unknown.

Aging and related health concerns: Benefit has been observed in patients with diabetes, obesity, and gingivitis; numerous preclinical studies suggest benefit for lifespan extension, cancer prevention/treatment, arthritis, cataract, and hypercholesteremia.

Types of evidence:

- 5 controlled clinical trials testing triphala mouthwash
- 3 clinical studies testing ingestion of triphala, 1 in healthy volunteers, 1 in diabetics, and 1 in obese subjects
- 1 open-label clinical study testing triphala mouthwash in boys with oral lesions
- Numerous laboratory studies

Lifespan: EXTENSION IN FLIES. A recent study in Drosophila flies showed that a symbiotic formulation that included probiotics and Triphala increased maximal lifespan by 65% (from 40 days to 66 days) [3]. The probiotic formulation included *Lactobacillus plantarum* (NCIMB 8826), *Lactobacillus fermentum* (NCIMB 5221) and *Bifidobacteria longum spp. infantis* (NCIMB 702255). The symbiotic formulation included the probiotics plus 0.5% of triphala powder (obtained from the Ayurvedic Pharmacy at Banaras Hindu University in Varanasi, India).

Multiple mechanisms may be involved in the observed lifespan extension. Both the probiotic and synbiotic formulations rescued markers of metabolic stress by managing insulin resistance and energy regulatory pathways. Compared to controls, individual probiotics, or triphala alone, the probiotic and synbiotic formulations significantly reduced body weight, triglyceride levels, and glucose levels. These formulations also prevented the elevations in inflammation, oxidative stress and the loss of mitochondrial complex integrity. In almost all the measured pathways, the synbiotic formulation had a more robust impact than its individual components, suggesting its combinatorial effect. It is still unclear how these findings translate to potential benefit in humans, as the gut microbiota is very different in flies compared to humans.

Cancer: POTENTIAL BENEFIT IN PRECLINICAL STUDIES. No clinical trials have tested the efficacy of triphala treatment in cancer patients.

A network pharmacology analysis has suggested that Triphala may inhibit proliferation of several cancer cell lines via diverse signaling pathways, including downregulation of MAPK/ERK, PI3K/Akt/mTOR, and NF-κB/p53 [4]. The triphala used was finely powdered containing equal proportions of the 3 fruits (Dabur India Ltd, Alwar, India, batch number AL1675).

There have been several other *in vitro* studies suggesting benefit of triphala in preventing or treating cancers. In 3 different cancer cell lines (cervical adenocarcinoma, pancreatic adenocarcinoma, and triple-negative breast carcinoma), triphala treatment induced programmed cell death by interfering with the assembly of microtubules (component of the cytoskeleton that provides cellular structure) [5]. A colon cancer cell culture study reported that triphala treatment suppressed proliferation by decreasing levels of proteins involved in proliferation (c-Myc and cyclin D1), and induced apoptosis through elevation of the pro-apoptotic Bax/Bcl-2 ratio [6]. In mice with drug-induced liver cancer, triphala treatment (5% in diet, w/w) for 2 weeks significantly decreased liver damage, lipid peroxidation, and also the activity of lactate dehydrogenase (LDH) in the liver [7]. Triphala simultaneously increased the

level of reduced glutathione (GSH) and the activity of glutathione-S-transferase (GST) thereby suggesting that it prevents peroxidative damage.

A 2010 review of the potential of triphala in preventing and treating cancer stated that the proposed mechanisms that are thought to underlie chemoprotective, radioprotective, and chemopreventive effects include: free radical scavenging properties, antioxidant effects, decreased cell damage, inhibition of lipid peroxidation, anti-inflammatory effects, antimutagenic effects, and immunomodulatory effects [2].

Prebiotic: POTENTIAL BENEFIT. An *in vitro* study using gut microbiota of 12 people who adhered to a vegetarian/vegan diet reported that triphala supplementation increased the abundance of many bacteria known to promote human health, including *Bifidobacterium spp*., *Lactobacillus spp.*, and *Bacteroides spp* [8]. Triphala induced large increases in the relative abundance of *Dorea*, *Sutterella*, *Phascolarctobacterium*, *Lactobacillus*, and *Butyrivibrio* (range = 116–580-fold). Smaller increases were observed for *Lachnoclostridium*, *Oscillibacter*, *Eubacterium*, *Roseburia*, and *Bacteroides* (range = 12–70-fold). While *Bacteroides* were only increased by 12-fold, this shift is highly significant since its final average relative abundance represented 24.5% of the community. Triphala supplementation also resulted in the reduced relative abundance of many species, including potential pathogens such as *Citrobacter freundii* and *Klebsiella pneumoniae*. Health benefits of triphala may be due, at least in part, to its ability to modulate the gut microbiota in a manner predicted to improve colonic epithelium function, reduce inflammation, and protect from opportunistic infection [8].

Inflammation: POTENTIAL BENEFIT. In a phase 1 clinical study of 20 healthy volunteers, triphala treatment (1,050 mg/day, orally) for 2 weeks resulted in significant immunostimulatory effects on cellular immune response, especially cytotoxic T cells and natural killer cells [9]. However, no significant changes in cytokine secretion (IL6, IFN-ɣ, TNFα) were detected.

An *in vitro* study of retinal-choroid microvascular endothelial cell culture reported that triphala and its bioactive compounds (chebulagic acid, chebulinic acid, and gallic acid) inhibited cell proliferation, migration, and pro-inflammatory activity (IL-6, IL-8, and MCP-1) without affecting cell viability [10]. This was mediated by inhibition of p38, ERK and NFκB phosphorylation. *In silico* studies revealed that chebulagic acid, chebulinic acid, and gallic acid are capable of binding to TNFα-receptor-1 to mediate anti-TNFα activity. Authors suggest that triphala may be protective against diabetic retinopathy and neovascular age-related macular degeneration.

A 2014 review on triphala and its bioactive compounds stated that triphala stimulates neutrophil function, enhances macrophage activation, and neutralizes reactive oxygen species [11].

Arthritis: POTENTIAL BENEFIT. Numerous studies in rodents have shown that triphala treatment (100 mg/kg) ameliorates arthritic symptoms, though no studies have tested triphala in arthritis patients. In arthritic rats (induced by complete Freund's adjuvant), triphala treatment showed anti-inflammatory effects by reducing inflammatory mediator (e.g. IL-17, COX-2, and RANKL) expression via inhibition of NF-κB activation [12]. In the same paper, a study in cell culture also showed that triphala significantly suppressed production of inflammatory mediators (e.g. TNFα, IL-1β, IL-6, MCP-1, VEGF, NO, PGE2), intracellular free radicals, and release of lysosomal enzymes (e.g. acid phosphatase, β-galactosidase, N-acetyl glucosamindase and cathepsin D) in a dose-dependent manner.

A study from the same group also reported that triphala ameliorated bone and cartilage degradation in arthritic rats by down-regulating pro-inflammatory cytokines, inflammatory marker enzymes, RANKL and transcription factors NF-kB and AP-1 [13]. Also, triphala treatment (100 mg/kg, i.p.) in arthritic mice reduced levels/activities of lipid peroxidation (~41.5%), glycoproteins (hexose ~43.3%, hexosamine ~36.5%, and sialic acid ~33.7%), and lysosomal enzymes (acid phosphatase ~52.4%, β-galactosidase ~22.9%, N-acetyl β-glucosaminidase ~22.1%, and cathepsin-D ~27.7%), while increasing antioxidant status (SOD ~75.6%, CAT ~62.7%, GPx ~55.8%, GST ~82.1%, and GSH ~72.7%) [14]. Similar to the studies above, inflammatory mediator levels in serum (TNF-α ~75.5%, IL-1β ~99%, VEGF ~75.2%, MCP-1 ~76.4%, and PGE2 ~69.9%) were suppressed with triphala in arthritic rats. Older studies in arthritic mice also reported similar results, with triphala treatment (1g/kg, orally) inhibiting inflammation, lipid peroxidation, and lysosomal enzyme release [15; 16].

Periodontitis/Gingivitis and oral lesions: BENEFIT. Numerous randomized controlled trials have shown that use of triphala mouthwash (0.6-6% concentration) for 14-60 days significantly reduces plaque, gingivitis, and halitosis [17; 18; 19; 20]. Triphala mouthwash was equally effective as chlorhexidine mouthwash, which is the gold standard in periodontitis treatment. Triphala mouthwash also significantly reduced oral microbial counts [20]. In a controlled trial of 60 undergraduate student volunteers, twice daily use of 6% triphala mouthwash for 7 days resulted in 44% reduction of oral streptococci colony forming units to a degree almost identical to that of chlorhexidine [21].

In an open-label clinical study of 34 teenage Indian boys with tobacco-induced oral lesions, 9 months of triphala mouthwash (0.6% concentration) significantly improved abnormal findings [22]. At baseline there were 16 normal and 11 abnormal smear reports (out of 27 boys), but after 9 months of triphala

mouth wash, there were 23 normal and 4 abnormal smears (e.g., keratosis). Biopsy report also showed that at baseline, 26 out of 27 had abnormal biopsy (hyperkeratinization, dyskeratosis, mild pleomorphism, or fibrous bands), but after 9 months, 23 had normal biopsy and only 4 had abnormal biopsy (hyperkeratinization or mild pleomorphism).

Cataract: POTENTIAL BENEFIT. No studies have tested the effect of triphala in people with cataract. A preclinical study reported that triphala significantly restored glutathione (antioxidant) levels and decreased malondialdehyde (oxidative stress marker) levels in a rat model of cataract (induced by selenite injection) [23]. A significant restoration in the activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione-s-transferase was observed in the triphala-supplemented group compared to controls. In a parallel *in vivo* study, only 20% developed cataract in triphala (25mg/kg)-treated rats, whereas 100% developed cataracts in untreated controls. Protective benefits are likely due to triphala's antioxidant activity.

Diabetes: BENEFIT. In a clinical study including 60 non-insulin-dependent diabetes mellitus patients, triphala treatment (5 g of powder mixed with buttermilk and taken 2 hours after dinner) for 45 days significantly reduced mean fasting blood glucose and postprandial glucose [24]. Mean fasting blood glucose went from 178 mg/dl at baseline to 137 mg/dl after 45 days. Postprandial glucose went from 242 at baseline to 209 mg/dl (control went from 243 to 255 mg/dl).

In mice fed a high-fat diet, supplementation with triphala (or its constituents) resulted in improved glucose levels and oral glucose tolerance [25].

Hypercholesteremia: POTENTIAL BENEFIT. In rats with experimentally-induced hypercholesteremia, triphala treatment (1g/kg) for 48 days prevented the increase in total cholesterol, LDL, VLDL, and free fatty acid to levels as low as control rats [26].

Obesity: BENEFIT. In a double-blind randomized controlled trial of 62 obese subjects, triphala treatment (5 g, twice daily, before breakfast and after dinner) resulted in significant reduction of body weight, waist circumference, and hip circumference [27]. The average weight loss was by 4.82 kg (95% CI, -3.52 to -6.11; from 96.89 to 92.52 kg), the mean reduction in waist circumference was 4.01 cm (95% CI, -2.13 to -5.90; from 116.0 to 112.4 cm), and the mean reduction in hip circumference was 3.21 cm (95% CI, -1.96 to -4.45; from 122.4 to 119.5 cm) in the triphala group. Mean fasting blood sugar and fasting serum insulin also significantly decreased in the triphala group compared to placebo, though blood pressure was not statistically different.

A few preclinical studies also support these findings. In mice fed a high-fat diet, supplementation with triphala (or its constituents) resulted in significant reductions in body weight, energy intake, and percentage of body fat [25]. Triphala also significantly improved lipid profiles of the mice by lowering serum total cholesterol, triglycerides, and LDL-cholesterol, and increasing levels of HDL-cholesterol. Triphala also reversed the pathological changes in liver tissue and decreased the relative weight of visceral adipose fat pads.

An *in vitro* study in an adipocyte cell line reported that an aqueous extract of triphala induced a concentration-dependent decrease in the intracellular lipid content and expression of both early and late phase adipogenic genes [28]. These results suggest that triphala prevents adipogenesis by downregulating lipid accumulation and expression of adipogenic genes.

Safety: Most clinical trials have used a mouthwash formulation of triphala for oral care; *in vitro* studies suggest that triphala mildly inhibits cytochrome P450 that metabolizes drugs and toxins.

Types of evidence:

- 3 clinical trials, of which were mouthwash formulations
- A few laboratory studies

Clinical trials: In a phase 1 clinical study in 20 healthy volunteers, ingestion of triphala extract (1,050 mg/day) for 2 weeks did not result in any adverse effects [9]. Routine laboratory data were also within normal (reference) ranges throughout the study.

Larger double-blind randomized controlled trials have been carried out, but these tested mouthwash formulations in people with periodontal diseases (e.g., gingivitis and plaque). Both of these studies reported no adverse events with triphala mouthwash for 2-3 weeks [17; 19].

Drug interactions: Drug interactions are not well-documented. Some websites mentioned that there are potential interactions with blood thinning medications such as warfarin (e.g., SuperFoodProfiles). Because *in vitro* studies suggest triphala mildly inhibits cytochrome P450 (by 23%), it may inhibit clearance of drugs normally metabolized by cytochrome P450 (particularly CYP2D6 and CYP3A4), resulting in accumulation of the drugs in the body and possible toxicity [29]. Though when compared to ketoconazole which is known to inhibit CYP2D6 and CYP3A4, they found that triphala's cytochrome P450 inhibition is mild and less likely to produce significant drug interactions.

Sources and dosing: Triphala is available OTC and can be purchased at health food stores and online. It consists of dried fruits from 3 plant species: *Emblica officinalis* (Amalaki), *Terminalia bellerica* (Bibhitaki), and *Terminalia chebula* (Haritaki)—they are usually mixed at a 1:1:1 ratio. Triphala comes in many forms including powder, capsule, and liquid. Traditionally it is ingested as tea (dissolving the powder in hot water). Charak, an Ayurvedic physician, promoted taking Triphala with honey and ghee, which he suggested may allow people to live for 100 years devoid of old age and diseases (Cakrapani Datta's Ayurveda dipica, 1st ed., 1976).

Only a few randomized controlled clinical trial results have been published, but doses used in these studies ranged from 1-10 g/day [9; 24; 27]. In clinical trials, triphala mouthwash formulations have been effective against gingivitis and oral lesions at concentrations ranging from 0.6% to 6% [17; 20; 21; 22].

Numerous factors including the source of herbs, processing, bioavailability, digestion, and absorption of herbal components can contribute to variability in efficacy [1]. This variability is partly due to inherent differences in gut microbiota that catalyze the biotransformation of the various triphala components.

Research underway: Based on ClinicalTrials.gov, there is currently 1 ongoing trial testing oral triphala and rubia cordifolia (flowering plant in the coffee family) on the gut microbiome and skin properties (NCT03477825). It is scheduled to be completed in March 2019.

Westfall's paper (Drosophila lifespan extension study; [3]) included data filed in a US provisional patent (62/629832) through a company which Susan Westfall and Satya Prakash are co-founders.

Search terms:
Pubmed, Google:

- + Alzheimer's, + dementia, + cognitive, + memory, + brain, + Bredesen, + ApoE4, + meta-analysis, + clinical trial, + safety

Websites visited for triphala:

- Clinicaltrials.gov (1 ongoing)
- Examine.com (0)
- Treato.com (0)
- DrugAge (0)
- Geroprotectors (0)

- Drugs.com (0)
- WebMD.com (0)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (0)
- Pharmapro.com (0)

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