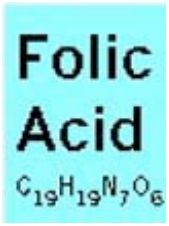
Folate (folic acid)



While some complementary and alternative techniques have been studied scientifically, high-quality data regarding safety, effectiveness, and mechanism of action are limited or controversial for most therapies. Whenever possible, it is recommended that practitioners be licensed by a recognized professional organization that adheres to clearly published standards. In addition, before starting a new technique or engaging a practitioner, it is recommended that patients speak with their primary healthcare provider(s). Potential benefits, risks (including financial costs), and alternatives should be carefully considered. The below monograph is designed to provide historical background and an overview of clinically-oriented research, and neither advocates for or against the use of a particular therapy.

Related Terms:

- B Complex vitamin, folacin, folate, folic acid, folinic acid, pteroylglutamic acid, pteroylmonoglutamic acid, pteroylpolyglutamate, vitamin B9, vitamin M.

BACKGROUND

- Folate and folic acid are forms of a water-soluble B vitamin. Folate occurs naturally in food and folic acid is the synthetic form of this vitamin. Folic acid is well-tolerated in amounts found in fortified foods and supplements. Sources include cereals, baked goods, leafy vegetables (spinach, broccoli, lettuce), okra, asparagus, fruits (bananas, melons, lemons), legumes, yeast, mushrooms, organ meat (beef liver, kidney), orange juice, and tomato juice. Folic acid is frequently used in combination with other B vitamins in vitamin B complex formulations.

SCIENTIFIC EVIDENCE

Uses *These uses have been tested in humans or animals. Safety and effectiveness have not always been proven. Some of these conditions are potentially serious, and should be evaluated by a qualified healthcare provider.*	Grade*
Folate deficiency Folate deficiency will occur if the body does not get the adequate amount of folic acid from dietary intake. Folic acid has been shown to be effective in the treatment of megaloblastic and macrocytic anemias due to folate deficiency.	A
Megaloblastic anemia - due to folate deficiency Folate deficiency can cause megaloblastic (or macrocytic) anemia. In this type of anemia, red blood cells are larger than normal, and the ratio of nucleus size to cell cytoplasm is increased. There are other potential causes of megaloblastic anemia, including vitamin B12 deficiency or various inborn metabolic disorders. If the cause is folate deficiency, then treatment with folate is the standard approach. Patients with anemia should be evaluated by a physician in order to diagnose and address the underlying cause.	A

underlying cause.	
Prevention of pregnancy complications Studies have proven that folate consumption during pregnancy prevents deficiency and anemia in pregnant women. Low folate levels during pregnancy may contribute to birth defects and pregnancy loss. Consuming a high dietary intake of folate and taking folic acid supplements orally during pregnancy reduces the risk of neural tube birth defects or cleft palate in the infant.	**A**
Methotrexate toxicity Folate supplementation is beneficial in patients being treated with long-term, low-dose methotrexate for rheumatoid arthritis (RA) or psoriasis. Development of folate deficiency is associated with increased risk of certain side effects including gastrointestinal effects, stomatitis, alopecia, abnormal liver function tests, myelosuppression, megaloblastic anemia, and increased homocysteine levels, which are associated with cardiovascular disease. People who have experienced side effects may need to continue taking folic acid for the duration of methotrexate therapy. Patients receiving methotrexate for cancer should avoid folic acid supplements, unless recommended by their oncologist. There is some evidence that folic acid supplements reduce the efficacy of methotrexate in the treatment of acute lymphoblastic leukemia, and theoretically they could reduce its efficacy in the treatment of other cancers.	**B**
Alzheimer's disease Preliminary evidence indicates that low folate concentrations might be related to Alzheimer's disease. Well-designed clinical trials of folate supplementation are needed before a conclusion can be drawn.	**C**
Arsenic poisoning (arsenic-induced illnesses) Folate may lower blood arsenic concentrations and thereby contribute to the prevention of arsenic-induced illnesses. Additional research is needed in this area.	**C**
Cancer Preliminary evidence surrounding the use of folate seems promising for decreasing the risk of breast, cervical, pancreatic, and gastrointestinal cancer. However, currently there is insufficient evidence available to recommend folate supplementation for any type of cancer prevention or treatment. Please follow the advice of a qualified healthcare provider in this area.	**C**

Chronic fatigue syndrome Some patients with chronic fatigue syndrome (CFS) also have decreased folic acid levels. Daily injections of a combination of folic acid, bovine liver extract, and vitamin B12 for three weeks were not beneficial for CFS in one study.	C
Depression Folic acid deficiency has been found among people with depression and has been linked to poor response to antidepressant treatment. Folate supplements have been used for enhancing treatment response to antidepressants. Limited clinical research suggests that folic acid is not effective as a replacement for conventional antidepressant therapy. Depression should be treated by a qualified healthcare provider.	C
Folate deficiency in alcoholics Folate deficiency has been observed in alcoholics. Alcohol interferes with the absorption of folate and increases excretion of folate by the kidney. Many alcohol abusers have poor quality diets that do not provide the recommended intake of folate. Increasing folate intake through diet, or folic acid intake through fortified foods or supplements, may be beneficial to the health of alcoholics.	C
Hearing loss (age-associated hearing decline) Folic acid supplementation slowed the decline in hearing of speech frequencies associated with aging in a population from a country without folic acid fortification of food. The effect requires confirmation, especially in populations from countries with folic acid fortification programs.	C
Nitrate tolerance Folic acid might prevent nitroglycerin-induced nitrate tolerance and cross tolerance to endothelial nitric oxide, which plays a role in blood pressure control. These conditions need to be treated by a qualified healthcare provider.	C
Phenytoin-induced gingival hyperplasia Early evidence shows that applying folic acid topically may inhibit gingival hyperplasia (overgrowth of gum tissue) secondary to phenytoin therapy. Oral folic acid supplementation has not been proven to be beneficial. More research is needed in this area.	C
Pregnancy-related gingivitis Based on preliminary data, applying folic acid topically may improve gingivitis in	C

Based on preliminary data, applying folic acid topically may improve gingivitis in pregnant women. Well-designed clinical trials are needed to confirm these results.	
Stroke Study results are mixed for the use of folate in stroke patients. Further research is needed in this area before a strong recommendation can be made.	**C**
Vascular disease / hyperhomocysteinemia Elevated homocysteine levels may be a marker of vascular disease. Preliminary data suggests that folic acid lowers homocysteine levels and might reduce the risk of vascular disease (cardiac, peripheral, or cerebral). Large randomized controlled trials are needed before a firm conclusion can be drawn.	**C**
Vitiligo Based on preliminary data, folic acid and vitamin B12 may improve the symptoms of vitiligo. Further research is needed to confirm these results.	**C**
Down's syndrome One study does not show a protective effect of folic acid on heart anomalies among infants with Down's syndrome.	**D**
Lometrexol toxicity Folic acid supplementation does not seem to reduce toxicity from the cancer drug lometrexol.	**D**
Fragile X syndrome Folic acid supplementation has been shown not to improve symptoms of fragile X syndrome.	**F**
Key to grades*: **A: Strong scientific evidence for this use; **B**: Good scientific evidence for this use; **C**: Unclear scientific evidence for this use; **D**: Fair scientific evidence against this use (it may not work); **F**: Strong scientific evidence against this use (it likely does not work).*	

TRADITION/THEORY

The below uses are based on tradition, scientific theories, or limited research. They often have not been thoroughly tested in humans, and safety and effectiveness have not always been proven. Some of these conditions are potentially serious, and should be evaluated by a qualified healthcare provider. There may be other proposed uses that are not listed below.

- AIDS, anti-aging (preventing signs of aging), aphthous ulcers, celiac disease, colorectal adenoma, Crohn's disease, diabetes (type 2), fracture (risk reduction), genetic damage (X-ray induced chromosomal damage), high blood pressure, infertility, insomnia, liver disease, macular degeneration, memory enhancement, osteoporosis, peripheral neuropathy, restless leg syndrome, sickle cell anemia, spinal cord injury (myelopathy), ulcerative colitis.

DOSING

The below doses are based on scientific research, publications, traditional use, or expert opinion. Many herbs and supplements have not been thoroughly tested, and safety and effectiveness may not be proven. Brands may be made differently, with variable ingredients, even within the same brand. The below doses may not apply to all products. You should read product labels, and discuss doses with a qualified healthcare provider before starting therapy.

Adults (over 18 year old)

- **U.S. Recommended Dietary Allowance (RDA) for adults (oral)**: 400 micrograms per day for males or females ages 14 years and older; 500 micrograms per day for breastfeeding adult women; 600 micrograms per day for pregnant adult women. Given as dietary folate equivalents (DFE).
- **Tolerable upper intake levels (UL) per day**: The UL is the maximum daily level of intake that is likely not to pose a risk of adverse effects. The UL is 800 micrograms per day for males or females ages 14-18 years-old (including pregnant or breastfeeding women); and 1,000 micrograms per day for males or females ages 19 years and older (including pregnant or breastfeeding women).
- **Adjunct treatment with conventional antidepressants**: Doses of 200 to 500 micrograms per day has been used for enhancing treatment response to antidepressants. Limited clinical research suggests that folic acid is not effective as a replacement for conventional antidepressant therapy.
- **Anticonvulsant-induced folate deficiency**: 15 milligrams (15,000 micrograms) daily has been used under the supervision of a qualified healthcare provider.
- **Cervical cancer**: 0.8 to 10 milligrams (800 to 10,000 micrograms) daily has been used but further data is necessary before a strong recommendation can be made.
- **Colon cancer**: Doses of 400 micrograms per day have been used to reduce the risk of colon cancer occurring, although supplementation has not been proven to be effective.
- **Drug-induced toxicity**: For reduction of toxicity symptoms (nausea and vomiting) associated with methotrexate therapy for rheumatoid arthritis (RA) or psoriasis, 1 milligram per day (1,000 micrograms per day) may be sufficient, but up to 5 milligrams per day (5,000 micrograms per day) may be used.
- **End stage renal disease (ESRD)**: Doses of 0.8 to 15 milligrams (800 to 15,000 micrograms) folic acid per day are generally used, but the degree of homocysteine reduction is very variable (between 12-50%), and normal homocysteine levels (<12 micromoles per liter) cannot always be achieved. Folic acid 2.5 to 5 milligrams (2,500 to 5,000 micrograms) three times weekly also reduces homocysteine levels in ESRD patients on dialysis. Doses greater than 15 milligrams (15,000 micrograms) per day do not provide additional benefit. Doses of 30 to 60 milligrams (30,000 to 60,000 micrograms) seem to cause a rebound in homocysteine levels when treatment is stopped.
- **Folate deficiency**: The typical dose is 250 to 1,000 micrograms per day. For severe folate

deficiency, such as in cases of megaloblastic anemia and malabsorption disorders, 1-5 milligrams (1,000 to 5,000 micrograms) per day is often used until corrected blood tests are documented by a qualified healthcare professional.

- **Hyperhomocysteinemia**: Doses of 0.5 to 5 milligrams per day (500 to 15,000 micrograms) have been used, although 0.8 to 1 milligrams per day (800 to 1,000 micrograms) appears to provide maximal reduction of homocysteine levels. Doses greater than 1 milligram per day (1,000 micrograms) do not seem to produce any greater benefit except in some people with certain gene mutations that cause homocysteine levels of 20 micromoles per liter or higher. However, initial data suggest that the U.S. Government-mandated fortification of cereals and flour with 140 micrograms folic acid per 100 grams is reducing the mean homocysteine level in the general population by about 7%. Consumption of at least 300 micrograms per day of dietary folate seems to be associated with a 20% lower risk of stroke and a 13% lower risk of cardiovascular disease when compared with consumption of less than 136 micrograms of folate per day. Doses of 10 milligrams (10,000 micrograms) per day of folic acid have been used to improve coagulation status, oxidative stress, and endothelial dysfunction.
- **Megaloblastic anemia**: In cases of megaloblastic anemia resulting from folate deficiency or malabsorption disorders such as sprue, oral doses of 1 to 5 milligrams (1,000 to 5,000 micrograms) per day may be used until hematologic recovery is documented by a qualified healthcare provider.
- **Neural tube defects (prevention)**: Doses of at least 400 micrograms of folic acid per day from supplements or fortified food should be taken by women capable of becoming pregnant and continued through the first month of pregnancy. Women with a history of previous pregnancy complicated by such neural tube defects usually take 4 milligrams (4,000 micrograms) per day beginning one month before and continuing for three months after conception under the guidance of a qualified healthcare professional.
- **Pancreatic cancer**: Consuming greater than 280 micrograms per day of dietary folate is associated with a decreased risk of exocrine pancreatic cancer. Further research is needed to confirm these results.
- **Phenytoin-induced gingival hyperplasia**: Applying folic acid topically may inhibit gingival hyperplasia secondary to phenytoin therapy. However, taking folic acid by mouth does not seem to be beneficial for this indication.
- **Pregnancy-related gingivitis**: Applying folic acid topically may improve gingivitis in pregnancy.
- **Preventing increases in homocysteine levels after nitrous oxide anesthesia**: Folate 2.5 milligrams (2,500 micrograms) in combination with pyridoxine 25 milligrams (25,000 micrograms) and vitamin B12 500 micrograms has been used daily for one week before surgery under the supervision of a qualified healthcare provider.
- **Vitiligo**: Doses of 5 milligrams (5,000 micrograms) have been taken twice daily to improve the symptoms of vitiligo.

Children (under 18 years old)

- **U.S. Recommended Dietary Allowance (RDA) or Adequate Intake (AI) for children (oral)**: For infants 0-6 months-old the AI is 65 micrograms per day; for infants 7-12 months-old the AI is 80 micrograms per day; for children 1-3 years-old the RDA is 150 micrograms per day; for children 4-8 years-old the RDA is 200 micrograms per day; for children 9-13 years-old the RDA is 300 micrograms per day. Given as dietary folate equivalents (DFE).
- **Tolerable upper intake levels (UL) per day**: The UL is the maximum daily level of intake that

is likely not to pose a risk of adverse effects. For children 1-3 years-old the UL is 300 micrograms; for children 4-8 years-old the UL is 400 micrograms; for children 9-13 years-old the UL is 600 micrograms; for adolescents 14-18 years-old the UL is 800 micrograms.

- **Caution**: Folic acid injection contains benzyl alcohol (1.5%) as a preservative and extreme care should be used in administration to neonates. Folic acid injections should be administered by a qualified healthcare provider.

SAFETY

The U.S. Food and Drug Administration does not strictly regulate herbs and supplements. There is no guarantee of strength, purity or safety of products, and effects may vary. You should always read product labels. If you have a medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy. Consult a healthcare provider immediately if you experience side effects.

Allergies

- Avoid folic acid supplements if hypersensitive or allergic to any of the product ingredients.

Side Effects and Warnings

- Folate appears to be well tolerated in recommended doses. Stomatitis, alopecia, myelosupression, and zinc depletion have been reported.
- An intravenous loading dose of folic acid, vitamin B6, and vitamin B12 followed by oral administration of folic acid plus vitamin B6 and vitamin B12, taken daily after coronary stenting, might actually increase restenosis rates. Due to the potential for harm, this combination of vitamins should not be recommended for patients receiving coronary stents.
- Erythema, pruritus, urticaria, skin flushing, rash, and itching have been reported.
- Nausea, bloating, flatulence, cramps, bitter taste, and diarrhea have been reported.
- Color of urine may become more intense.
- Folic acid may mask the symptoms of pernicious, aplastic, or normocytic anemias caused by vitamin B12 deficiency and may lead to neurological damage.
- Irritability, excitability, general malaise, altered sleep patterns, vivid dreaming, overactivity, confusion, impaired judgment, increased seizure frequency, and psychotic behavior have been reported. Very high doses can cause significant central nervous system (CNS) side effects. Supplemental folic acid might increase seizures in people with seizure disorders, particularly in very high doses.
- Anaphylaxis and bronchospasm have also been reported.

Pregnancy and Breastfeeding

- **Pregnancy**: It is recommended that all women capable of becoming pregnant consume folate in order to reduce the risk of the fetus developing a neural tube defect. Folic acid supplementation in higher than recommended doses is categorized as FDA Pregnancy Category C.
- **Breastfeeding**: Folic acid is present in the breast milk and is likely safe to use during breastfeeding under the supervision of a qualified healthcare provider.

INTERACTIONS

Most herbs and supplements have not been thoroughly tested for interactions with other herbs, supplements, drugs, or foods. The interactions listed below are based on reports in scientific publications, laboratory experiments, or traditional use. You should always read product labels. If you have a medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy.

Interactions with Drugs

- Excessive use of alcohol increases the requirement for folic acid.
- Aminosalicylic acid can reduce dietary folate absorption, worsening the folate deficiency often seen with active tuberculosis, or preventing its reversal during treatment. Megaloblastic anemia occurs rarely and usually when there are other contributing factors, such as concurrent vitamin B12 malabsorption. Patients being treated for tuberculosis may be advised to take folic acid supplements if their dietary folate intake is low.
- Chronic use of large doses of antacids can reduce folic acid absorption, but this is likely only significant if dietary folate intake is very low. Maintenance of the recommended daily intake of folic acid in the diet is recommended.
- Antibiotic therapy can disrupt the normal gastrointestinal (GI) flora, interfering with the absorption of folic acid. Folate supplements are not considered necessary.
- Aspirin may decrease serum folate levels, especially with chronic large doses. It is suggested that folate is just being redistributed in the body rather than an actual folate deficiency; therefore folate supplementation is not considered necessary.
- Oral contraceptives (birth control pills) may impair folate metabolism producing depletion, but the effect is unlikely to cause anemia or megaloblastic changes.
- Carbamazepine (Tegretol®) can reduce serum folate levels, but megaloblastic anemia has not been reported. Pregnant women taking carbamazepine may be especially at risk from reduced folate levels.
- Chloramphenicol may antagonize some effects of folic acid on the blood (hematopoietic system).
- Cholestyramine reduces folic acid absorption. It can lower serum and red blood cell folate levels in children taking large doses for several months. Maintenance of dietary folate intake is recommended.
- Colestipol (Colestid®) can interfere with absorption of folic acid, and reduced serum folate levels may occur. Maintenance of dietary folate intake is recommended.
- Cycloserine can reduce serum folate levels, and rare cases of megaloblastic anemia have occurred. Maintenance of dietary folate intake is recommended.
- Limited data suggests that diuretics ("water pills") may increase excretion of folic acid. Reduced red blood cell folate levels, possibly contributing to increased homocysteine levels, a risk factor for cardiovascular disease, were found in one group of people taking diuretics for six months or longer. The need for folic acid supplementation during diuretic therapy requires further study before a firm recommendation can be made. Currently, maintenance of dietary folate intake is recommended.
- Reduced serum and red blood cell folate levels can occur in some women taking conjugated estrogens (Premarin®), but this is unlikely in women with adequate dietary folate intake. Supplements are recommended only for those women with inadequate dietary intake or other conditions that contribute to folate deficiency, and for those diagnosed with, or at increased risk for, cervical dysplasia (due to family history for example).
- Folic acid absorption from the small intestine is optimal at pH 5.5 to 6. The increased pH

associated with the use of H2 blockers (such as cimetidine (Tagamet®), famotidine (Pepcid®), nizatidine (Axid®), and ranitidine (Zantac®)) may therefore reduce folic acid absorption, but this is probably only significant if dietary folate intake is very low. Another class of prescription drugs that may affect folic acid absorption is proton pump inhibitors (PPIs). These are used for reflux disease and ulcers and include esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Prilosec®), pantoprazole (Protonix®), and rabeprazole (Aciphex®). Maintenance of dietary folate intake is recommended.

- Reduced vitamin B12 and, to a lesser extent, folate levels occur in some people with diabetes and can contribute to hyperhomocysteinemia, which adds to their already increased risk of cardiovascular disease. The reduced folate levels seen in diabetics have been linked to metformin use in some cases, possibly as a result of reduced folic acid absorption. Symptomatic folate deficiency is unlikely to occur with metformin, but people with diabetes may need folic acid supplements to reduce hyperhomocysteinemia. Diabetes should be treated by a qualified healthcare provider.
- Methotrexate is a folate antagonist that prevents the conversion of folic acid to its active form, and lowers plasma and red blood cell folate levels. Folic acid supplements reduce side effects without reducing the efficacy of methotrexate in treating rheumatoid arthritis or psoriasis. Patients being treated with methotrexate for cancer should avoid folic acid supplements, unless recommended by their oncologist. Folic acid could interfere with the anticancer effects of methotrexate.
- Reduced serum folate levels have been noted in people with multiple sclerosis (MS) after treatment with methylprednisolone sodium succinate (Solu-Medrol®). Clinical significance is unknown.
- Chronic cigarette smoking is associated with diminished folate status.
- Folate-dependent enzymes have been inhibited in laboratory experiments by certain NSAIDs (ibuprofen (Advil®, Motrin®, Nuprin®), naproxen (Anaprox®, Aleve®), indomethacin (Indocin®), and sulindac (Clinoril®). Clinical significance is unknown.
- Reduced folate levels can occur in some people taking pancreatic extracts (such as Pancrease®, Cotazym®, Viokase®, Creon®, Ultrase®) possibly due to reduced absorption. Folate levels should be checked in patients taking pancreatic enzymes for prolonged periods.
- Pentamidine is a prescription drug used to treat *Pneumocystis carinii* pneumonia (PCP). Decreased serum folate levels and megaloblastic bone marrow changes can occur rarely with prolonged intravenous pentamidine (Pentacarinat®, Pentam 300®) therapy. Most patients are unlikely to need folic acid supplements.
- Phenobarbital (Luminal®) and primidone (Mysoline®) can reduce serum folate levels, occasionally leading to megaloblastic anemia (usually in people with low dietary folate intake), and possibly contributing to neurological side effects, mental changes, and cerebral atrophy. Pregnant women taking phenobarbital or primidone may be especially at risk from reduced folate levels. Folic acid can have direct convulsant activity in some people, reversing the effects of phenobarbital or primidone and worsening seizure control. Folic acid may increase metabolism of phenobarbital. Seizure activity should be monitored closely.
- Pyrimethamine (Daraprim®) is a folate antagonist that prevents conversion of folic acid to its active form. Patients taking pyrimethamine should avoid folic acid supplements since they can antagonize the therapeutic effects against *Toxoplasmosis* and *Pneumocystis carinii* pneumonia. Patients taking lower doses of pyrimethamine for prolonged periods should maintain the recommended dietary folate intake and monitored for folate deficiency. Folic acid does not antagonize the effects of pyrimethamine in the treatment of malaria. Folinic acid may

be used as an alternative to folic acid when indicated. Pyrimethamine also reduces serum folate levels.

- One study found that administration of folic acid to pregnant women might not interfere with the protective effect of sulfadoxine/pyrimethamine combination when used for intermittent preventative treatment of malaria.
- Sulfasalazine inhibits absorption and metabolism of folic acid. Patients on chronic sulfasalazine therapy may be advised to increase their dietary folate intake, and to take a supplement if they have any other condition, which could also contribute to deficiency.
- Triamterene (Dyrenium®) is a folate antagonist that prevents conversion of folic acid to its active form, and also reduces folate absorption. Reduced serum and red blood cell folate levels have occurred, and occasional cases of megaloblastic anemia, usually in people with other conditions contributing to folate deficiency. Patients on chronic triamterene therapy should to maintain the recommended dietary folate intake, or take a supplement if advised by their physician.
- There is a general belief that folic/folinic acid supplements do not interfere with the therapeutic effects of trimethoprim. However, this view has been challenged, and failure of trimethoprim therapy has occurred rarely when folinic acid is given concurrently.

Interactions with Herbs and Dietary Supplements

- Reduced serum and red blood cell folate levels can occur in some women taking conjugated estrogens (Premarin®) or birth control pills, but this is unlikely in women with adequate dietary folate intake. Theoretically this interaction may occur with estrogenic herbs and supplements as well.
- Taking folic acid along with vitamin B12 may increase the risk of vitamin B12 deficiency. Caution is advised when taking both of these vitamins together.
- Normal supplemental doses of folic acid are unlikely to have an adverse effect on zinc balance in people with adequate dietary zinc intake. The data on the effects of supplemental folic acid on dietary zinc absorption are conflicting.

AUTHOR INFORMATION

- This information is based on a systematic review of scientific literature edited and peer-reviewed by contributors to the Natural Standard Research Collaboration (www.naturalstandard.com).

REFERENCES

Natural Standard developed the above evidence-based information based on a thorough systematic review of the available scientific articles. For comprehensive information about alternative and complementary therapies on the professional level, go to www.naturalstandard.com. Selected references are listed below.

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