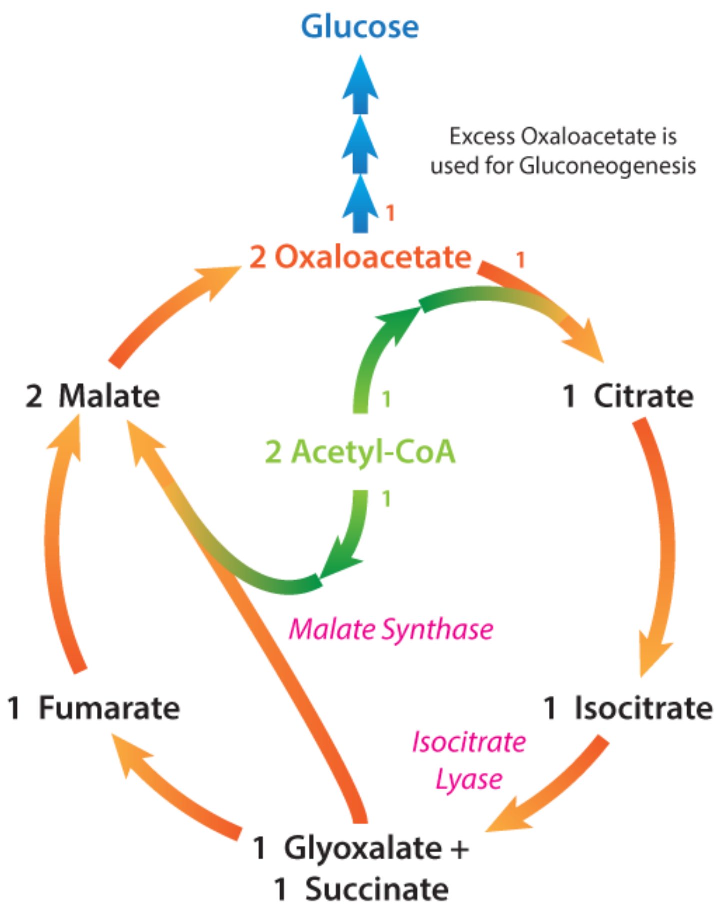
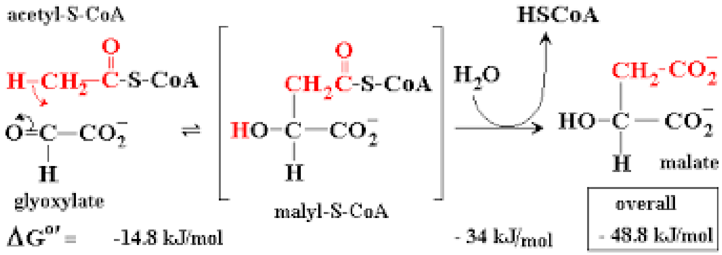
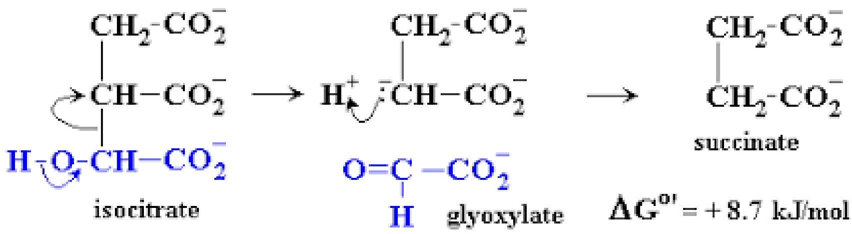
Glyoxylate cycle

The glyoxylate cycle, a variation of the tricarboxylic acid cycle, is an anabolic pathway occurring in plants, bacteria, protists, and fungi. The glyoxylate cycle centers on the conversion of acetyl-CoA to succinate for the synthesis of carbohydrates. In microorganisms, the glyoxylate cycle allows cells to use two carbons (C2 compounds), such as acetate, to satisfy cellular carbon requirements when simple sugars such as glucose or fructose are not available.



In plants the glyoxylate cycle occurs in special peroxisomes which are called glyoxysomes. This cycle allows seeds to use lipids as a source of energy to form the shoot during germination. The seed cannot produce biomass using photosynthesis because of lack of an organ to perform this function.



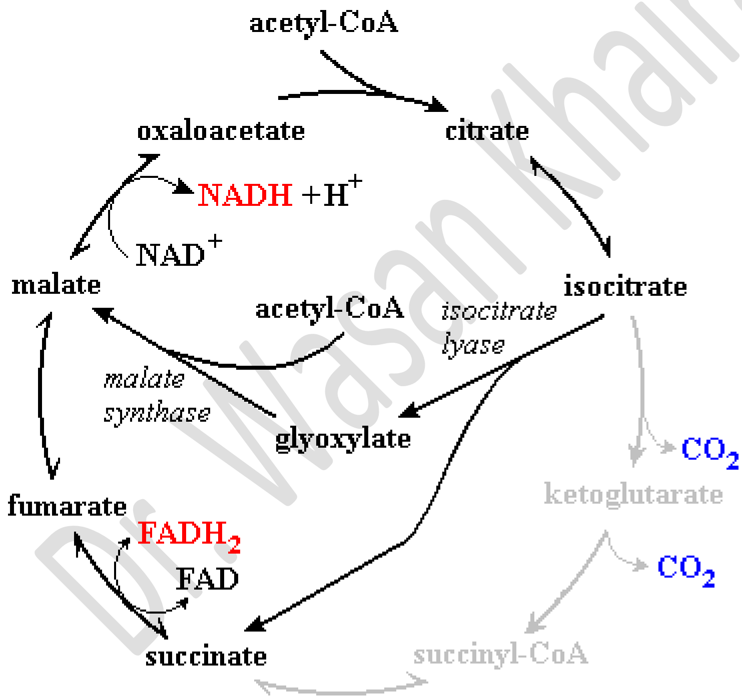


Plants as well as some algae and bacteria can use acetate as the carbon source for the production of carbon compounds. Plants and bacteria employ a modification of the TCA cycle called the glyoxylate cycle to produce four carbon dicarboxylic acid from two carbon acetate units. The glyoxylate cycle bypasses the two oxidative decarboxylation reactions of the TCA cycle and directly converts isocitrate through isocitrate lyase and malate synthase into malate and succinate.

The glyoxylate cycle uses five of the eight enzymes associated with the tricarboxylic acid cycle: **citrate synthase, aconitase, succinate dehydrogenase, fumarase, and malate dehydrogenase.** The two cycles differ in that in the glyoxylate cycle, isocitrate is converted into glyoxylate and succinate by isocitrate lyase (ICL) instead of into α-ketoglutarate. This bypasses the decarboxylation steps that take place in the citric acid cycle (TCA cycle), allowing simple carbon compounds to be used in the later synthesis of macromolecules, including glucose. Glyoxylate is subsequently combined with acetyl-CoA to produce malate, catalyzed by malate synthase. Malate is also formed in parallel from succinate by the action of succinate dehydrogenase and fumarase.

Cell-wall containing organisms, such as plants, fungi, and bacteria, require very large amounts of carbohydrates during growth for the biosynthesis of complex structural polysaccharides, such as cellulose, glucans, and chitin. In these organisms, in the absence of available carbohydrates (for example, in certain microbial environments or during seed germination in plants), the glyoxylate cycle permits the synthesis of glucose from lipids via acetate generated in fatty acid β-oxidation.

The glyoxylate cycle bypasses the steps in the citric acid cycle where carbon is lost in the form of CO2. The two initial steps of the glyoxylate cycle are identical to those in the citric acid cycle: acetate → citrate → isocitrate. In the next step, catalyzed by the first glyoxylate cycle enzyme, isocitrate lyase, isocitrate undergoes cleavage into succinate and glyoxylate (the latter gives the cycle its name). Glyoxylate condenses with acetyl-CoA (a step catalyzed by malate synthase), yielding malate. Both malate and oxaloacetate can be converted into phosphoenolpyruvate, which is the product of phosphoenolpyruvate carboxykinase, the first enzyme in gluconeogenesis. The net result of the glyoxylate cycle is therefore the production of glucose from fatty acids. Succinate generated in the first step can enter into the citric acid cycle to eventually form oxaloacetate.



Function in organisms(Plants)

In plants the glyoxylate cycle occurs in special peroxisomes which are called glyoxysomes. This cycle allows seeds to use lipids as a source of energy to form the shoot during germination. The seed cannot produce biomass using photosynthesis because of lack of an organ to perform this function. The lipid stores of germinating seeds are used for the formation of the carbohydrates that fuel the growth and development of the organism.

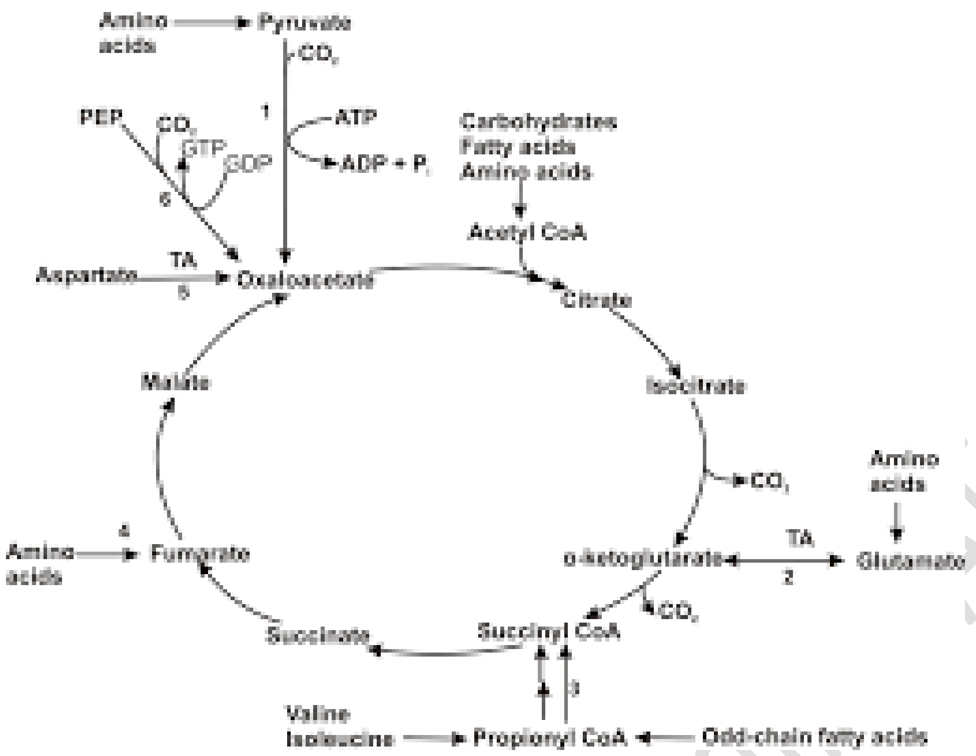
The glyoxylate cycle can also provide plants with another aspect of metabolic diversity. This cycle allows plants to take in acetate both as a carbon source and as a source of energy. Acetate is converted to acetyl CoA (similar to the TCA cycle). This acetyl CoA can proceed through the glyoxylate cycle, and some succinate is released during the cycle. The four carbon succinate molecule can be transformed into a variety of carbohydrates through combinations of other metabolic processes; the plant can synthesize molecules using acetate as a source for carbon. The acetyl CoA can also react with glyoxylate to produce some NADPH from NADP+, which is used to drive energy synthesis in the form of ATP later in the electron transport chain.

Pathogenic fungi

The glyoxylate cycle may serve an entirely different purpose in some species of pathogenic fungi. The levels of the main enzymes of the glyoxylate cycle, ICL and MS, are greatly increased upon contact with a human host. Mutants of a particular species of fungi that lacked ICL were also significantly less virulent in studies with mice compared to the wild type. The exact link between these two observations is still being explored, but it can be concluded that the glyoxylate cycle is a significant factor in the pathogenesis of these microbes.

Inhibition of the glyoxylate cycle

Due to the central role of the glyoxylate cycle in the metabolism of pathogenic species including fungi and bacteria, enzymes of the glyoxylate cycle are current inhibition targets for the treatment of diseases. Most reported inhibitors of the glyoxylate cycle target the first enzyme of the cycle (ICL). Inhibitors were reported for Candida albicans for potential use as antifungal agents. The mycobacterial glyoxylate cycle is also being targeted for potential treatments of tuberculosis.


Amino acids
Pyruvate
CO_2
1
ATP
ADP + P_i
PEP
CO_2
GTP
GDP
6
Carbohydrates
Fatty acids
Amino acids
Acetyl CoA
Aspartate
TA
5
Oxaloacetate
Citrate
Isocitrate
Malate
CO_2
Amino acids
4
Fumarate
α-ketoglutarate
TA
2
Glutamate
CO_2
Succinate
Succinyl CoA
3
Valine
Isoleucine
Propionyl CoA
Odd-chain fatty acids