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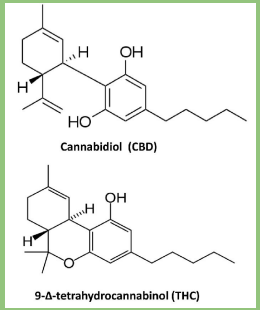
Biosynthesis of Cannabinoids in *S. cerevisiae*

Micah Smith, Southern Maine Community College

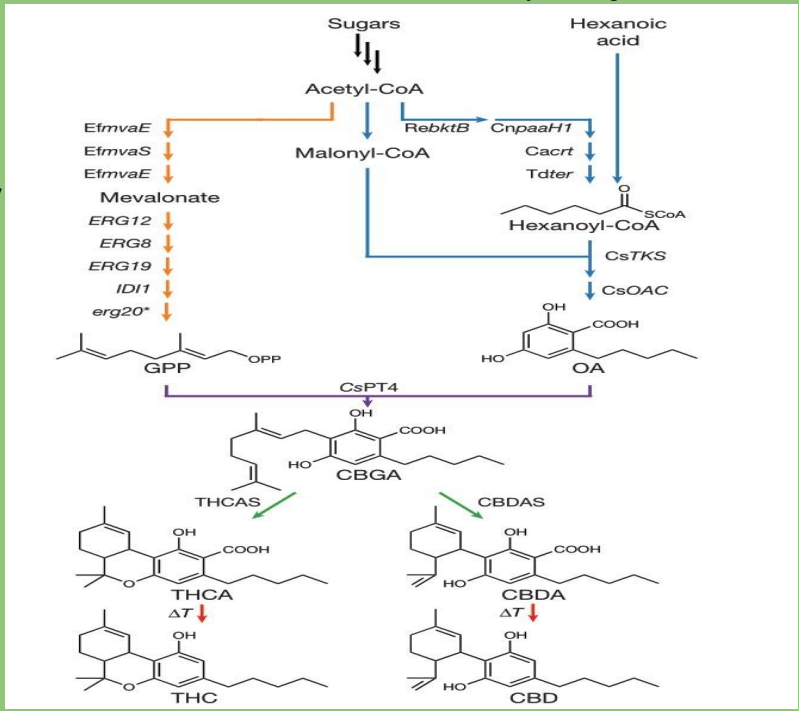
Abstract:
THC, CBD, and other cannabinoids have modern and historical uses in medicine. Studying these cannabinoids has been challenging due to the classification of these substances as narcotics and due to legal issues surrounding the plant, Cannabis sativa.
This literature review discusses some of the manipulations and modifications of biosynthetic pathways in Saccharomyces cerevisiae that have been done by researchers. Genes from Cannabis sativa and other organisms have been added to yeast so that enzymes are produced to metabolize THC and other cannabinoids from simple sugars.
Modifying an organism to produce certain chemical substances is more complex than modifying an organism to code for a particular polypeptide. Occasionally novel substances not found in nature are produced.
The development of reliable, lab-sustainable production of known and new biochemicals has great potential.

Introduction:

The medicinal uses of *Cannabis*, also known as marijuana, have been rediscovered by doctors, biologists, and health experts across the globe. As more governments decriminalize and legalize medical and/or personal use of the plant and its derived chemical substances, THC and CBD. As the organism becomes more accessible to obtain legally, there is an increase in demand for these substances for research purposes.
The development of new sources of THC, CBD, and other cannabinoids as research chemicals requires a means of producing them in the laboratory environment for manipulation and study.
A team of scientists genetically modified a strain of brewer's yeast (*S. cerevisiae*) to produce delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as well as novel cannabinoids that are not naturally occuring in the *Cannabis* plant. The development of this pathway not only allows for the compounds to be produced without the need of the plant, but also exists as a means to modify the existing pathways in the plant to produce the new cannabinoids in higher quantity and quality.

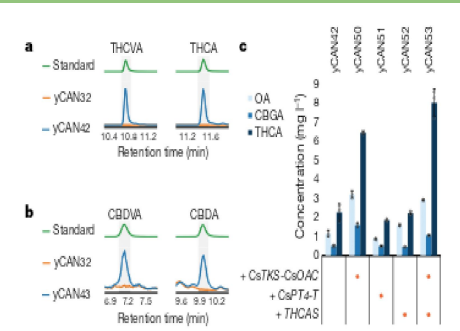


THC and CBD: The primary active compounds that produce the psychoactive and calming effects of *Cannabis*.



The biosynthetic pathway of the cannabinoid producing genetically engineered brewer's yeast (S. cerevisiae). The genes that encoded for specific enzymes were taken from different origin organisms and inserted into the yeast genome, in addition to using the organism's own existing enzymes. The yeast convert sugars and hexanoic acid into the component parts and assemble the cannabinoid precursor molecule, which is then broken down into different cannabinoids via different enzymes.

(Fig.1, Luo X., et al., 2019)



(Fig. 3, Luo X., et al., 2019)

Cannabinoid production via artificially-created biosynthetic pathways in yeast currently faces a problem with yield of the desired substances.

Biosynthetic pathways can produce substances that could potentially be harmful to the survival of a cell in great quantities. Most biosynthetic pathways have a type of feedback inhibition built-in to prevent such a fate. In many cases, the final product of the chain acts to inhibit the first enzyme in the chain by binding to an allosteric receptor site on the first enzyme. This causes the active site of the enzyme to change shape and subsequently its function, stopping or slowing the biosynthetic pathway until concentration of the final product is low enough that there isn't enough of the final product binding to enough of the first enzyme, at which point the cycle continues and repeats. Even artificially-created biosynthetic pathways are subject to feedback-inhibition limits.
Multiple copies of the pathway enzyme genes were introduced to later strains of yeast produced by the researchers. An increase in the number of copies of the enzyme showed increases in concentration of the final product with each additional copy providing a successively smaller increase in final concentration.

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