Bergamottin and its Role as a Drug Inhibitor

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Introduction

Bergamottin is a member of the furanocoumarin family and is most commonly found in grapefruit juice. Bergamottin is a known drug inhibitor of cytochrome P450 34A. For this reason, it is often recommended that patients avoid consumption of grapefruit juice if currently prescribed medication such as statins, antihistamines, and drugs in several other classes. This drug interaction is often referred to as “the grapefruit effect” and can cause the compound to remain in the body for a prolonged period of time; which may ultimately lead to health risks in some patients. The occurrence of bergamottin, the synthesis and biosynthesis of the compound will be discussed in the following review.

Figure 1. Bergamottin, a furanocoumarin found in grapefruit juice.

I. Occurrence

Bergamottin is a furanocoumarin compound found naturally in members of the Citrus Genus. It is most commonly associated with the Citrus × paradisi species, otherwise known as grapefruit, but this compound was originally identified in the Citrus bergamia, or Bergamot fruit. The Citrus × paradisi trees are classified as subtropical trees, and are therefore found in warmer climates; such as the southern portion of the United States, Barbados and Southeast Asia. The Citrus × paradisi species originated in Barbados as a hybrid between the Citrus maxima, a pomelo, and a Citrus sinensis, an orange. This explains the similarities of the grapefruit composition and the pomelo composition; both have drug inhibitory effects.

Figure 2. Citrus × paradisi and Citrus maxima. source (http://www.chefdecuisine.com/all_fruit/citrus/grapefruit/images/grapefruit_440x330.jpg)

The Citrus bergamia also grows in warmer climates and was initially found in Southeast Asia. Citrus bergamia is often found in Earl Grey tea. This species is the namesake of bergamottin, and it was in the bergamot orange that the compound was first isolated.

II. Biological Activity

Bergamottin inhibits the cytochrome P450 34A enzyme. Grapefruit juice was first noticed to cause such an inhibition when it was used as an additive to ease the consumption of the drug felodipine, which was mixed with ethanol and therefore had a very strong taste. It was observed that there was in fact a compound in the grapefruit juice that was causing this cytochrome P450 34A enzyme inhibition to be targeted, and an increase in the oral bioavailability was clearly taking place.

To validate this observation, in vitro experimentation was conducted to determine what compounds in grapefruit juice were causing this inhibition. It was postulated that three compounds could be causing this effect; naringin, 6',7'-dihydroxybergamottin, and bergamottin. These same experiments were then conducted in vivo and it turned out that bergamottin did in fact inhibit the cytochrome P450 34A enzyme in the body, whereas the other two compounds did not have any effect on the enzyme. This in vivo inhibition occurs in both the liver and the small intestine; these are the active sites for the effected drugs. There are many drugs that are able to be metabolized by the cytochrome P450 34A enzyme, so the inhibition of this enzyme may be a cause for concern; although the results from this inhibition are not always considered to have negative effects.

The oral bioavailability of the drugs become much longer when bergamottin inhibits the cytochrome P450 34A enzyme, and this can be further illustrated with the area under the time versus concentration curve, or the AUG, is taken into account. When the cytochrome P450 34A enzyme is not inhibited, this area under the curve is smaller than when bergamottin is present in the human system. This increase in oral bioavailability can be considered a positive effect when drugs such as Viagra or the anti-AIDS drug, saquinavir, are being prescribed. This is due to the fact that the desirable effects of these drugs will last for a longer period of time. The drug saquinavir has an undesirably low oral bioavailability on its own, but with help from bergamottin, the drug is much more effective. Patients taking drugs related to statins, such as Mevacor (lovastatin) and Lipitor (atorvastatin calcium), or antihistamines, such as terfenadine, should be...
of grapefruit juice consumption. There have been reports of serious undesirable side effects when these types of drugs are taken with grapefruit juice. These adverse effects are caused by the drug remaining in the biological system for a longer period of time than the drug is meant to, leading to a presystemic elimination, which eventually leads to the possibility of a patient overdose.

There are many different brands of grapefruit products containing bergamottin, ranging everywhere from doubly concentrated frozen grapefruit juice to grapefruit flavoured soda, and each brand contains a different amount of the compound. This means that various brands can be less effective than others when inhibiting the cytochrome P450 34A enzyme. People can also be affected differently by bergamottin depending on the amount cytochrome P450 34A enzyme. Inhibition of this enzyme can have both positive and negative effects as it elongates the oral bioavailability for the drugs that act at this site. The consumption of grapefruit products, as well as other bergamottin containing citrus products, especially grapefruit juice should be avoided in patients taking drugs that already have good oral bioavailabilities, as this can lead to a drug overdose. Studies are being conducted to reduce the content of bergamottin in grapefruit juice so that patients concerned with the effect of this compound on their prescribed drug regimens can once again enjoy such food commodities.

III. Biosynthesis

The biosynthesis of bergamottin is shown in figure 4. First, the demethylsuberosin (3) product is formed by the cyclization of the umbelliferone (2) compound, which originates from the shikimate pathway. This is done with the use of DMAPP (1), dimethylallyl pyrophosphate, which is an isomer of IPP, isopentenyl pyrophosphate, innate in most all living things. Next, a cyclization of the newly added alkyl group occurs to form marmesin (4). This process uses NADPH and oxygen along with a cytochrome P450 mono-oxygenase catalyst. This same catalyst and these same reagents are then used twice more, first to remove the hydroxyisopropyl substituent from marmesin (4) to form psoralen (5), and then to add a hydroxyl group to form bergaptol (6). Bergaptol (6) can then be methylated with SAM, S-Adenosylmethionine, to form bergapten (7). Finally, a GPP, or geranyl pyrophosphate, unit attaches itself to the newly methylated bergapten (7) to form the target molecule bergamottin (8).

IV. Synthesis

The synthetic approach to making bergamottin is shown in figure 5. The synthesis of this compound was unknown for a number of years after it was first isolated, but this approach now produces the compound with an extremely high yield of 98%. This synthesis is initiated by combining the commercially available starting product, bergapten (9), with magnesium diiodide, MgI$_2$. In this effect works to demethylate the bergapten (9) and forms the bergaptol (10) product with a yield of 87%. The bergaptol (10) is then alkylated using the phase transfer conditions that make selective alkylation possible. This reaction forms the bergamottin product with a 98% yield.

Figure 5. Synthesis of Bergamottin

Conclusion

Bergamottin has proven very effective as a cytochrome P450 34A inhibitor. Inhibition of this enzyme can have both positive and negative effects as it elongates the oral bioavailability for the drugs that act at this site. The consumption of grapefruit products, as well as other bergamottin containing citrus products, especially grapefruit juice should be avoided in patients taking drugs that already have good oral bioavailabilities, as this can lead to a drug overdose. Studies are being conducted to reduce the content of bergamottin in grapefruit juice so that patients concerned with the effect of this compound on their prescribed drug regimens can once again enjoy such food commodities.
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