Cloning and Expression of Ginkgo biloba Levopimaradiene Synthase

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Technology description

Ginkgo biloba leaf extracts have been used for centuries to treat cerebrovascular and cardiovascular diseases. Recently, the American Medical Association endorsed the Chinese herb as a viable alternative to traditional approaches in the treatment of Alzheimer's Disease. Recent studies report that the extract delayed the progression of dementia in approximately one third of the patients studied. The beneficial pharmacological effects imparted by the extract are believed to be due, in part, to the ginkgolides, a unique series of diterpene natural products produced by Ginkgo biloba. Furthermore, the ginkgolides have been found to be highly-specific platelet-activating factor (PAF) receptor antagonists. Generation of PAF occurs during anaphylaxis or shock and leads to bronchoconstriction, contraction of smooth muscle, and reduced coronary blood flow, and can be fatal. Ginkgolide B is the most active of the diterpenes and antagonizes all known PAF induced membrane events.

Presently, the commercial development of the ginkgolides as therapeutic agents has been stunted due to the topological and stereochemical complexities involved in diterpene synthesis. Current commercial ginkgolide production relies exclusively on extraction from Ginkgo trees, which accumulate low levels of the compound. Although multiple total synthesis of (Â±)-ginkgolide A and ginkgolide B have been reported, the multi-step syntheses are plagued by low yields, which precludes commercial-scale synthesis.

Rice researchers have successfully cloned and characterized the enzyme, levopimaradiene synthase, which catalyzes the first committed step in ginkgolide biosynthesis. This gene is essential to genetic engineering approaches to overproduce ginkgolides. Specifically, levopimaradiene synthase is needed to produce the ginkgolide precursor levopimaradiene. Potential levopimaradiene production methods claimed here include in vitro conversion of geranylgeranyl pyrophosphate (GGPP), and in vivo production (in Ginkgo or microorganisms) using biosynthetic GGPP at native levels or in organisms genetically modified to have high GGPP levels. Levopimaradiene synthase overexpression in Ginkgo will allow higher levels of more advanced ginkgolide precursors to be realized.

Further, expression in organisms that natively produce GGPP, and that express genes encoding enzymes that metabolize GGPP will allow production of ginkgolide or ginkgolide precursors. Additional information available upon request.

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