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Bavachinin, as a novel natural pan-PPAR agonist, exhibits unique synergism with synthetic PPAR-γ and -α agonists in anti-diabetic and hypolipidemic effects

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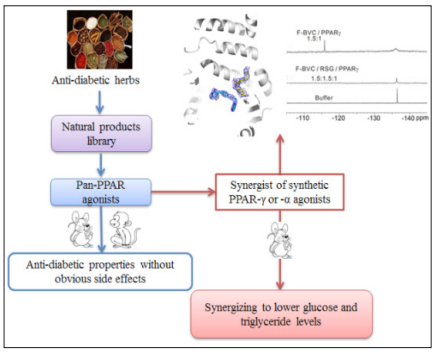
Statement of the Problem: Pan-peroxisome proliferator-activated receptors (PPAR) agonists have long been desired as therapeutics against metabolic syndrome, but available PPAR agonists currently show limited efficacy and adverse effects. Natural herbs provide a structurally untapped resource to prevent and treat complicated metabolic syndrome.



Methodology & Theoretical Orientation: Natural PPAR agonists were evaluated using reporter gene, competitive binding and 3T3-L1 pre-adipocyte differentiation assays *in vitro*. The effects in metabolic phenotyping were verified in db/db and diet induced obese mice. In addition, we studied synergistic actions of Bavachinin plus synthetic PPAR-γ or -α agonists through nuclear magnetic resonance, molecular docking, reporter gene and mouse model.

Findings: Bavachinin, as a novel natural pan-PPAR agonist, exhibited anti-diabetic properties without weight gain and hepatotoxicity. Importantly, Bavachinin synergized with synthetic PPAR-γ agonists thiazolidinediones and -α agonists fibrates to induce PPAR transcriptional activities as well as to lower glucose and triglyceride levels in db/db mice. We further found that Bavachinin has a novel alternate binding site besides the same canonical site as one of thiazolidinediones-rosiglitazone and it can block Bavachinin binding to this canonical site but not to the novel site.

Conclusion & Significance: Bavachinin is a novel natural pan-PPAR agonist from the traditional Chinese anti-diabetic herb Malaytea scurfpea fruit. This is the first time to report synergistic anti-diabetic and hypolipidemic effects between Bavachinin and synthetic agonists induced by different binding sites in PPAR-γ or -α. Their combination may improve efficacy and decrease toxicity of marketed drugs for use as adjunctive therapy to treat metabolic syndrome.

Recent Publications

1. Rubenstrunk A, Hanf R, Hum D W, Fruchart J C and Staels B (2007) Safety issues and prospects for future generations of PPAR modulators. Biochimica et. *Biophysica Acta;* 1771: 1065-1081.
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4. Matin A, Doddareddy M R, Gavande N, et al. (2013) The discovery of novel isoflavone pan peroxisome proliferator-activated receptor agonists. Bioorganic & Medicinal Chemistry; 21: 766-778.
5. Choi J H, Banks A S, Kamenecka T M, et al. (2011) Antidiabetic actions of a non-agonist PPAR-gamma ligand blocking Cdk5-mediated phosphorylation. *Nature;* 477: 477-481.

Biography

Li Feng has her expertise in natural products drug discovery for improving metabolic syndrome with extensive knowledge on pharmacology, molecular biology, structural biology and medicinal chemistry. Her natural compound library based on specialized herbs creates new structurally untapped resource for improving healthcare. Based on this library, she has discovered many promising natural lead compounds targeted to nuclear receptors and enzymes and has applied dozens of national and international patents. Some of the invention patents have been transformed to pharmaceutical company.

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