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## Metabolic engineering for enhanced terpenoid production: Leveraging new horizons with an old technique

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## ABSTRACT

Terpenoids are a vast class of plant specialized metabolites (PSMs) manufactured by plants and are involved in their interactions with environment. In addition, they add health benefits to human nutrition and are widely used as pharmaceutically active compounds. However, native plants produce a limited amount of terpenes restricting metabolite yield of terpene-related metabolites. Exponential growth in the plant metabolome data and the requirement of alternative approaches for producing the desired amount of terpenoids, has redirected plant biotechnology research to plant metabolic engineering, which requires in-depth knowledge and precise expertise about dynamic plant metabolic pathways and cellular physiology. Metabolic engineering is an assuring tool for enhancing the concentration of terpenes by adopting specific strategies such as overexpression of the key genes associated with the biosynthesis of targeted metabolites, controlling the modulation of transcription factors, downregulation of competitive pathways (RNAi), co-expression of the biosynthetic pathway genes in heterologous system and other combinatorial approaches. Microorganisms, fast-growing host plants (such as Nicotiana benthamiana), and cell suspension/callus cultures have provided better means for producing valuable terpenoids. Manipulation in the biosynthetic pathways responsible for synthesis of terpenoids can provide opportunities to enhance the content of desired terpenoids and open up new avenues to enhance their production. This review deliberates the worth of metabolic engineering in medicinal plants to resolve issues associated with terpenoid production at a commercial scale. However, to bring the revolution through metabolic engineering, further implementation of genome editing, elucidation of metabolic pathways using omics approaches, system biology approaches, and synthetic biology tactics are essentially needed.

## 1. Introduction

Plants can synthesize a vast variety of metabolites, which are fundamental to their growth and reproduction and are known as primary metabolites. Additionally, plants also produce some trivial differentiating plant specialized metabolites (PSMs) in small amounts which are not essential for basic vegetative growth and reproduction, however, they provide evolutionary and ecological advantages and help plants defend against biotic stresses such as deterring herbivores and pathogens, and impart them adaptive properties to survive during abiotic stresses (Jahangeer et al., 2021). These metabolites also perform paramount adaptive functions in the life cycle of the plants facilitating pollination and seed dispersal. These taxa/species-specific PSMs were considered functionless in the past. However, plant-based natural products have a multitude of applications and have been used for pharmaceutical purposes to treat serious ailments, since time immemorial, in the form of crude extracts. Plethora of drugs including antimalarial, anticholinergics, anticancer, immunosuppressive, and

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