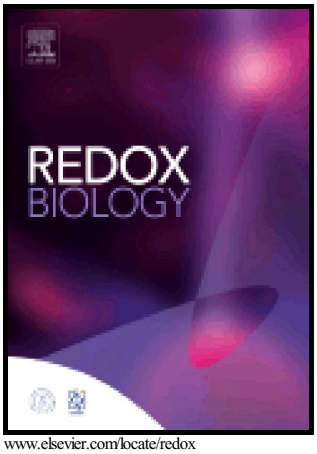


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# Identification of novel Nrf2 activators from *Cinnamomum chartophyllum* H. W. Li and their potential application of preventing oxidative insults in human lung epithelial cells

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## Abstract

Human lung tissue, directly exposed to the environmental oxidants and toxicants, is apt to be harmed to bring about acute or chronic oxidative insults. The nuclear factor erythroid 2-related factor 2 (Nrf2) represents a central cellular defense mechanism, and is a target for developing agents against oxidative insult-induced human lung diseases. Our previous study found that the EtOH extract of *Cinnamomum chartophyllum* protected human bronchial epithelial cells against oxidative insults via Nrf2 activation. In this study, a systemic phytochemical investigation of the aerial parts of *C. chartophyllum* led to the isolation of thirty chemical constituents, which were further evaluated for their Nrf2 inducing potential using NADP(H): quinone reductase (QR) assay. Among these purified constituents, a sesquiterpenoid bearing α, β-unsaturated ketone group, 3*S*-(+)-9-oxonerolidol (NLD), and a diphenyl sharing phenolic groups, 3, 3', 4, 4'-tetrahydroxydiphenyl (THD) significantly activated Nrf2 and its downstream genes, NADPH: quinone oxidoreductase 1 (NQO-1), and γ-glutamyl cysteine synthetase (γ-GCS), and enhanced the nuclear translocation and stabilization of Nrf2 in human lung epithelial cells. Importantly, NLD and THD had no toxicity under the Nrf2 inducing doses. THD also demonstrated a potential of interrupting Nrf2-Keap1 protein−protein interaction (PPI). Furthermore, NLD and THD protected human lung epithelial cells against sodium arsenite [As(III)]-induced cytotoxicity. Taken together, we conclude that NLD and THD are two novel Nrf2 activators with potential application of preventing acute and chronic