# Fighting fat and inflammation: Scientists develop new compounds

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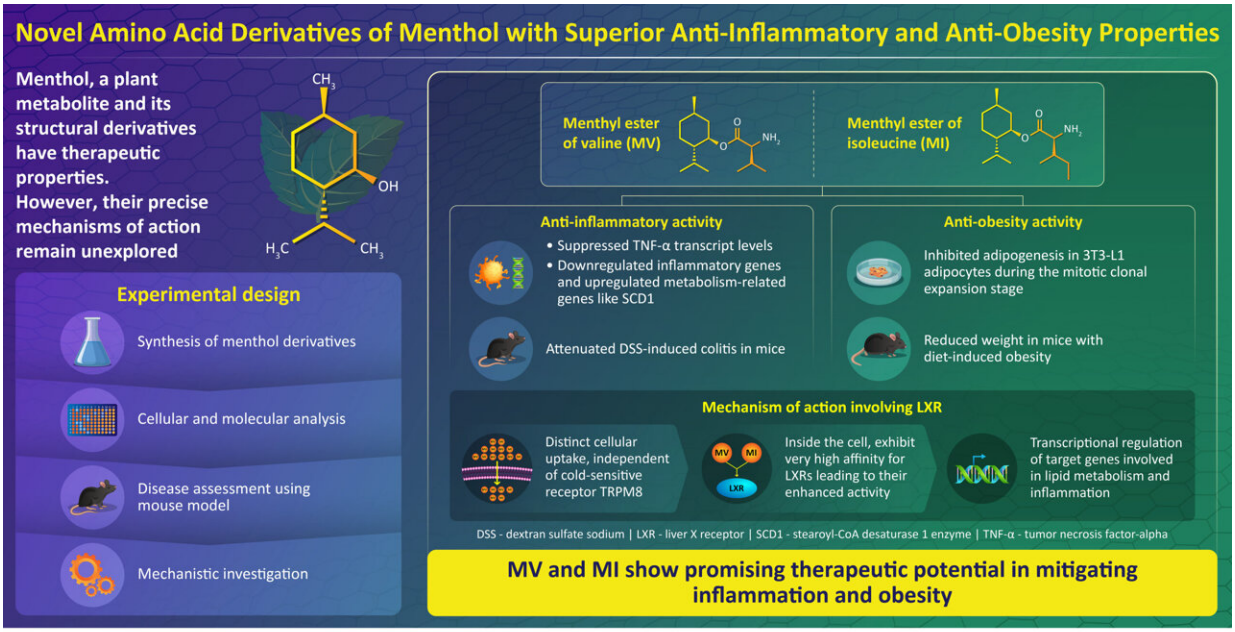


The menthyl esters of valine (MV) and isoleucine (MI) are multi-faceted molecules with enhanced anti-inflammatory and anti-obesity activities. The discovery and development of such molecules can result in newer classes of therapeutic drugs to treat a wide range of metabolic disorders. Credit: Gen-ichiro Arimura from Tokyo University of Science

Modified derivatives of natural products have led to significant therapeutic advances and commercial success in recent times. Menthol is

a naturally occurring cyclic monoterpene alcohol found in various plants, particularly in members of the mint family such as peppermint and spearmint. It is a common ingredient found in a wide range of confectionaries, chewing gums and oral care products. Interestingly, menthol also has high medicinal value due to its analgesic, anti-inflammatory, and anti-cancer effects.

In a recent study, a team of researchers led by Professor Gen-ichiro Arimura from the Department of Biological Science and Technology, Tokyo University of Science, Japan, developed and investigated menthyl esters of valine (MV) and isoleucine (MI), which are derived from menthol by replacing its hydroxyl group with valine and isoleucine, respectively.

Their research findings were published in the journal *Immunology* on May 8, 2024.

Sharing the motivation behind the present work, Prof. Arimura says, "The functional components of plants that contribute to human health have always intrigued me. Discovering new molecules from natural materials inspired our research team to develop these amino acid derivatives of menthol."

The researchers began by synthesizing menthyl esters of six amino acids characterized by less-reactive side chains. Subsequently, they assessed the properties of these esters using in vitro cell line studies. Finally, they conducted experiments in mice to explore the effects of these compounds under induced disease conditions. The exceptional anti-inflammatory profiles of MV and MI was determined by assessing the transcript levels of tumor necrosis factor-α (Tnf) in stimulated macrophage cells.

Remarkably, both MV and MI outperformed menthol in the anti-

inflammatory assay. RNA sequencing analysis revealed that 18 genes involved in inflammatory and immune responses were effectively suppressed.

The researchers went a step further and investigated the mechanism of action of the menthyl esters. They discovered that liver X receptor (LXR)—an intracellular nuclear receptor, had an important role in the anti-inflammatory effects and this was independent of the cold-sensitive transient receptor TRPM8, which primarily detects menthol.

Delving deeper into the LXR-dependent activation of MV and MI, they found that Scd1 gene—central to lipid metabolism was upregulated by LXR. Moreover, in mice with induced intestinal colitis, the anti-inflammatory effects were further validated with suppressed transcript levels of Tnf and Il6 genes by MV or MI, in an LXR-dependent manner.

Driven by the discovery of LXR-SCD1 intracellular machinery, Prof. Arimura and his team hypothesized the menthyl esters possess anti-obesity properties. They found that these esters inhibited adipogenesis-fat accumulation, specifically at the mitotic clonal expansion stage in 3T3-L1 adipocyte cells. During animal studies, the diet-induced obesity in mice was ameliorated and adipogenesis was suppressed.

Menthyl esters possess unique advantages compared to other anti-inflammatory or anti-obesity compounds currently being researched or used. Their specific mechanisms of action, which contribute to their dual anti-inflammatory and anti-obesity effects, sets them apart from other compounds and may make them particularly effective in addressing both inflammatory conditions and metabolic disorders. They could benefit specific populations like individuals with chronic inflammatory conditions, metabolic syndrome, or obesity-related complications.

"Although this study focused on their functions and mechanisms of

action in diseases modeled after inflammation and obesity, we expect that these compounds will also be effective against a wide range of lifestyle-related diseases caused by metabolic syndrome, such as diabetes and hypertension, as well as allergic symptoms," says Prof. Arimura optimistically.

In conclusion, this study underscores the importance and value of multi-faceted molecules derived from naturally occurring substances. Future research involving these novel and superior menthyl esters may result in therapeutic compounds to tackle the ever-growing health concerns of obesity and inflammatory conditions.

**More information:** Seidai Takasawa et al, The powerful potential of amino acid menthyl esters for anti-inflammatory and anti-obesity therapies, *Immunology* (2024). DOI: 10.1111/imm.13798

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