Towards sustainable lipidomics: computational screening and experimental validation of chloroform-free alternatives for lipid extraction

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Abstract

Sample preparation, particularly lipid extraction, plays a critical role in lipidomics workflows and strongly influences analytical outcomes. In biomedical research, the most commonly used lipid extraction protocols rely on chloroform due to its favorable physicochemical properties, including the ability to dissolve both polar and apolar lipids, as well as its high volatility. Although well-established chloroform-based methods enable high recovery of a broad range of lipids, concerns about the toxicity and environmental impact of chloroform necessitate the development of more sustainable alternatives. In this study, a combined computational and experimental strategy was employed to identify and validate greener solvents suitable for lipid extraction in lipidomics applications. Solvent selection was guided by Hansen solubility parameters, Abraham solvation descriptors, and principal component analysis, yielding five candidate solvents as potential chloroform alternatives. Evaluation of solvent sustainability and human health risk was conducted using CHEM21 criteria and supplemented by a comprehensive literature review. Initial validation of extraction efficiency for identified candidates was performed using synthetic lipid standards in the absence of a biological matrix, followed by testing lipid extraction from human plasma using both monophasic and biphasic extraction protocols. The highest extraction efficiency was achieved using a single-phase extraction method based on cyclopentyl methyl ether, which exhibited comparable and even superior performance to the conventional chloroform-based Folch protocol. Overall, this study highlights the feasibility of replacing chloroform with less hazardous solvents in lipidomics workflows without compromising analytical performance, and provides a comparative assessment of computational solvent prediction approaches for green chemistry applications.