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Applications of stable isotope ratio analysis and site-specific natural isotope fractionation-nuclear magnetic resonance in discriminating between synthetic and natural analogs

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Consumers today are increasingly seeking products containing molecules of natural origin, as these are often perceived as healthier compared to their synthetic or semi-synthetic counterparts. However, the higher costs associated with the production of plant-based raw materials, as well as the extraction and purification of these natural substances, create opportunities for counterfeiting. This often involves the addition of cheaper, chemically indistinguishable synthetic forms. Techniques such as Stable Isotope Ratio Mass Spectrometry (SIRA) and Site-Specific Natural Isotope Fractionation by Nuclear Magnetic Resonance (SNIF-NMR) are valuable tools for distinguishing molecules of natural, biosynthetic, or synthetic origin across various categories, including flavorings, essential oils, foodstuffs, dietary supplements, pharmaceuticals, and steroids. While both methods are expensive and require specialized equipment, SNIF-NMR is less accessible and more complex than SIRA. However, it provides more detailed, site-specific molecular information. Despite the high precision and sensitivity of SNIF-NMR, SIRA offers broader scientific applications but is challenged by complex data interpretation and the limited availability of reference materials. Among isotopic parameters, δ^{2}H measured by IRMS or (D/H)n determined via SNIF-NMR has demonstrated the greatest ability to discriminate, generally showing lower values in natural molecules and more positive ones in their synthetic counterparts. Although δ^{13}C is the most extensively studied parameter, it does not always provide significant discrimination between natural and synthetic fossil-derived products. Nevertheless, it is particularly effective for differentiating natural molecules extracted from specific plants and their biosynthetic analogs, which are synthesized from C4 substrates such as sugarcane and corn (e.g., red yeast rice or L-theanine). In specific cases, δ^{15}N (e.g., for caffeine) and δ^{18}O (e.g., for *Serenoa repens* extract) have shown excellent potential for characterization.