

ANNONACEOUS ACETOGENINS: A REVIEW

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ABSTRACT.—The Annonaceous acetogenins are a series of apparently polyketide-derived fatty acid derivatives that possess tetrahydrofuran rings and a methylated γ -lactone (sometimes rearranged to a methyl ketolactone) with various hydroxyl, acetoxy, and/or ketoxy groups along the hydrocarbon chain. They exhibit a broad range of potent biological activities (cytotoxicity, antitumor, antimalarial, antimicrobial, immunosuppressant, antifeedant, and pesticidal). The sources, isolation, chemistry, biogenesis, and biological actions of these compounds, published to date, are tabulated and discussed. Strategies for structural elucidation are reviewed, and structural revisions and refinements are suggested for some of the previously published compounds.

The Annonaceae is a large family of tropical and subtropical trees and shrubs comprising about 120 genera and more than 2000 species (1). The phytochemistry of the Annonaceae through 1982 has been reviewed by Leboeuf *et al.* (2). Their review details the various alkaloids, carbohydrates, lipids, amino acids, proteins, polyphenols, essential oils, terpenes, and aromatic compounds typically found in these plants. Many species in this family are used in traditional medicine for various purposes; however, most of the previous phytochemical studies have not attempted to explain these folkloric uses through testing of biological activities. Bioactivity-directed isolation studies are strongly suggested in the search for potentially useful bioactive secondary metabolites in all medicinal plants.

Such an activity-directed fractionation by Jolad *et al.* (3), using 3PS *in vivo* murine leukemia testing of an EtOH extract of the roots of *Uvaria accuminata*, led to the isolation and structural elucidation of uvaricin, an unusual antitumor compound. Uvaricin was thus the first example of a new class of extremely bioactive compounds that are now referred to as the Annonaceous acetogenins. Chemically, these are C₃₅–C₃₈ compounds, apparently of polyketide origin, possessing one or two tetrahydrofuran rings and a γ -lactone (either saturated or unsaturated), usually involving a three-carbon chain attached to a long aliphatic chain, and having long unbranched aliphatic regions that are variously hydroxylated, acetoxy, or ketonized. We predict that additional chemical variations exist and will be found in the future.

The purpose of this review is to present the sources, isolation, chemistry, possible biogenesis, and biological activities of this rapidly growing class of natural compounds. Some helpful structural elucidation strategies and techniques for the determination of the stereochemistries of these typically waxy and amorphous acetogenins, via spectroscopic means, are presented. Also, a number of structural revisions and refinements of previously published compounds are suggested.

STRUCTURAL CLASSES

Three structural classes are currently evident when considering the number and arrangement of the tetrahydrofuran rings. For purposes of this review, the discussion is organized on the basis of these structural classes. It is quite possible that new classes exist and are awaiting discovery. The structures, physical and spectral data, bioactivities, sources, and references are presented in tabular form; ¹³C-nmr assignments, if available, are provided around the structural illustrations of each compound. Explanations of the tabular footnotes and abbreviations used for the biological activities are pre-