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Therapeutic Potential of Natural Acetogenins: Extraction Techniques, Pharmacological Activities, and Future Applications

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ABSTRACT

Acetogenins, a unique class of secondary metabolites primarily found in the Annonaceae family, exhibit remarkable pharmacological properties, particularly as potent cytotoxic and anticancer agents. This systematic review synthesizes recent advancements in acetogenin research, focusing on extraction methodologies, biological activities, and therapeutic applications. A structured literature search spanning 2010–2024 was conducted across PubMed, Scopus, Web of Science, and Google Scholar, adhering to PRISMA guidelines. The findings highlight the efficacy of acetogenins in inhibiting cancer cell proliferation, particularly in breast, colorectal, and brain cancers, through mitochondrial inhibition and apoptosis induction. Recent innovations, including ultrasonic-assisted extraction and nanoparticle-based formulations, have significantly improved bioavailability and therapeutic outcomes. Despite these promising developments, challenges such as low solubility, potential neurotoxicity, and limited clinical validation persist. Future research should prioritize the optimization of drug delivery systems and in-depth clinical trials to establish acetogenins as next-generation natural anticancer agents.

Key words: acetogenins; cancer therapy; ctotoxicity; apoptosis; drug delivery; ntural products.

INTRODUCTION

Natural compounds have long served as a foundation for drug discovery, particularly in oncology. Among these bioactive molecules, acetogenins—a distinct class of polyketides primarily derived from the Annonaceae family—have gained increasing attention due to their potent cytotoxic and anticancer properties. These compounds, including annonacin, squamocin, and bullatacin, exhibit selective toxicity against cancer cells by inhibiting mitochondrial complex I, disrupting ATP synthesis, and inducing apoptosis. Such mechanisms make acetogenins promising candidates for anticancer drug development (Mangal *et al*., 2015; Shi *et al*., 2020; Parra *et al*., 2021).

Cancer remains one of the leading causes of mortality worldwide, necessitating the continuous search for effective therapeutics with reduced side effects. Conventional chemotherapy often suffers from multidrug resistance (MDR) and systemic toxicity, prompting interest in natural alternatives such as acetogenins. These compounds have demonstrated significant in vitro and in vivo anticancer activity against various malignancies, including breast, colorectal, gastric, glioblastoma, and leukemia. Beyond their anticancer potential, acetogenins have also shown antimicrobial, antioxidant, and anti-inflammatory properties, broadening their pharmacological relevance

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(Suresh *et al*., 2011; Mangal *et al.*, 2015; Kuete *et al*., 2016; Esselin *et al*., 2017; Han *et al*., 2019; Ando *et al*., 2022).

Despite their promising bioactivity, the clinical translation of acetogenins remains limited due to challenges such as poor water solubility, low bioavailability, and potential neurotoxicity. Recent advancements in extraction techniques, purification strategies, and drug delivery systems—such as nanoparticle-based formulations and liposomal encapsulation—have aimed to overcome these limitations. Furthermore, the structural modification of acetogenins has led to the development of synthetic derivatives with improved pharmacokinetics and selectivity (Liaw *et al*., 2016; Lima *et al*., 2022).

This systematic review provides a comprehensive analysis of acetogenins, focusing on their pharmacological activities, extraction methodologies, and therapeutic applications in cancer treatment. By synthesizing research findings from the past decade, this review identifies key trends, research gaps, and future directions. Through an in-depth exploration of their molecular mechanisms and drug development potential, this study highlights acetogenins as promising candidates for next-generation cancer therapeutics.

MATERIALS AND METHODS

This systematic literature review (SLR) followed PRISMA guidelines to synthesize data on acetogenins, focusing on their pharmacological activities, extraction methods, and therapeutic applications in cancer treatment. A structured search across PubMed, Scopus, Web of Science, and Google Scholar (2010–2024) was conducted using Boolean operators and relevant keywords. Studies were selected based on predefined inclusion criteria (e.g., pharmacological studies, extraction techniques, in vitro/in vivo research) and excluded if they lacked methodological details, focused solely on plant taxonomy, or were non-peer-reviewed (Page *et al*., 2021).

Data extraction included study characteristics, source plants, bioactivities, mechanisms of action, and therapeutic implications. A narrative synthesis approach was employed to identify research trends and gaps. To ensure reliability, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used for quality assessment. Despite potential limitations (e.g., language restrictions, study variability), this review provides a comprehensive and structured evaluation of acetogenins, highlighting their potential as next-generation natural anticancer agents.

RESULTS AND DISCUSSION

Global Trends and Country Contributions in Acetogenin Research: Advances, Challenges, and Future Directions

Research on acetogenins has expanded significantly over the past decade, with increasing global interest in their pharmacological applications, particularly in cancer therapy. Between 2010 and 2015 (Figure 1), studies primarily focused on isolation and chemical characterization of acetogenins from Annonaceae plants, with China, Japan, and Mexico leading in identifying bioactive compounds from *Annona* species (Rodríguez-Sánchez *et al*., 2019). During 2016 to 2019, research diversified to include molecular mechanisms of action, nanoparticle-based drug formulations, and in vivo studies on animal models. China pioneered investigations into nanotechnology-enhanced bioavailability, whereas Brazil, Mexico, and Indonesia focused on optimizing natural extraction techniques and exploring additional pharmacological properties such as antioxidant and anti-inflammatory effects (Hadisaputri *et al*., 2021).

From 2020 onward, research on acetogenins has surged with advancements in drug delivery systems, clinical applications, and toxicity studies. China, Egypt, and Brazil have explored their therapeutic potential in gastrointestinal, breast, and brain cancers, while Japan and Mexico have prioritized safety and toxicity evaluations (Sousa

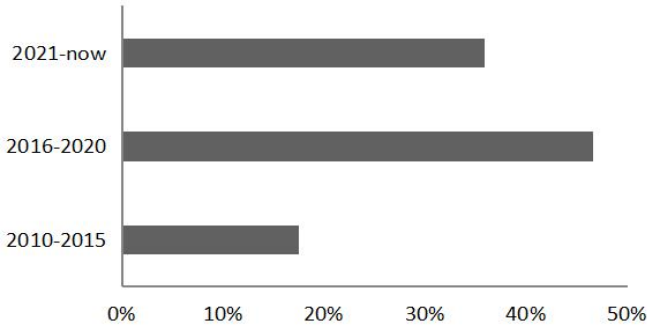

Figure 1. Percentage of acetogenin research from 2010-2024.

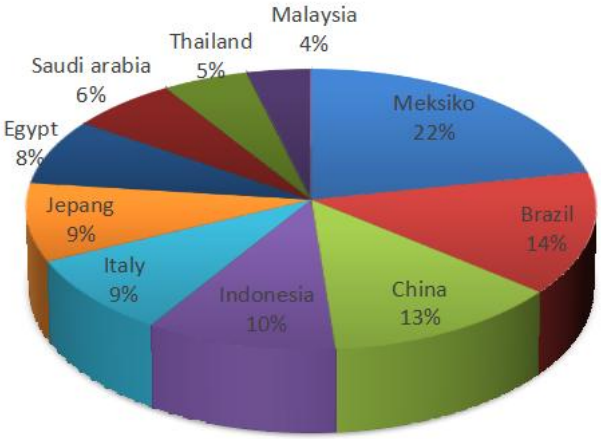

Figure 2. Percentage of countries researching acetogenins.

et al., 2023). Indonesia and Brazil continue to refine ultrasound-assisted and microwave-assisted extractions, enhancing acetogenin yield and purity (Hadisaputri *et al*., 2021). In terms of global contributions, Mexico (17%), Brazil (11%), and China (10%) (Figure 2) have led in acetogenin research, followed by Indonesia (8%), Italy, and Japan (7% each) (Page *et al*., 2021). These trends highlight an evolving research landscape where technological advancements and interdisciplinary collaborations are driving acetogenins toward pharmaceutical development, with future efforts needed to enhance clinical validation and address bioavailability challenges (Rodríguez-Sánchez *et al*., 2019).

Availability of Plants as a Source of Acetogenins

Research on acetogenins has demonstrated that plants from the genus Annona are the primary sources of these compounds, with *Annona muricata* (soursop) being the most extensively studied species, recorded in 30 studies (Damayanti *et al*., 2019; Geisler *et al*., 2019; Md Roduan, Abd Hamid & Mohtarrudin, 2019; Virgen-Ceceña *et al*., 2019; Iwo, Alfaridzi & Muhammad, 2023; Chan *et al*., 2024). The predominance of *A. muricata* (Pinto *et al*., 2018; Artanti *et al*., 2020; Ogbu *et al*., 2020; Astuti *et al*., 2021)in research is likely due to its high acetogenin content and its potential as an anticancer agent. Additionally, other species within the Annona genus, such as *A. cherimola* (Teresa Gutiérrez *et al*., 2020; Al Kazman *et* al., 2023; Gastric *et al*., 2023; González-Reyna *et al*., 2024; Li *et al*., 2024)and *A. squamosa* (Costa *et al*., 2014; Lima *et al*., 2022; Mokhtar *et al*., 2022; Al Kazman, Harnett & Hanrahan, 2023), have also garnered significant attention, with four studies each. Meanwhile, other species like *A. macroprophyllata* (Laguna Hernández *et al*., 2015; Brechú-Franco *et al*., 2016; Rendón-Barrón *et al*., 2024) and *A. mucosa* (Ribeiro *et al*., 2014, 2015)have been investigated to a lesser extent, with three and two studies, respectively (Hadisaputri *et al*., 2021).

Beyond the Annona genus, other plants within the Annonaceae family have also been the focus of research, such as *Goniothalamus chinensis* (Duc *et al*., 2016) and *Polyalthia debilis* (Boonpangrak *et al*., 2015). These plants contain unique acetogenins that exhibit cytotoxic activity against cancer cells and antimicrobial properties. However, studies on these species remain relatively limited compared to Annona (Figure 3), suggesting that their potential has yet to be fully explored (Rodríguez-Sánchez *et al*., 2019).

Outside the Annonaceae family, plants from the Lauraceae family (Feng *et al*., 2022; Freitas *et al*., 2022), particularly *Persea americana* (avocado) (Colin-Oviedo *et al*., 2022; Freitas *et al*., 2022), have attracted attention as alternative sources of acetogenins. Research on avocado has shown that acetogenins present in its fruit and seeds exhibit strong antioxidant activity and potential applications in treating inflammatory and

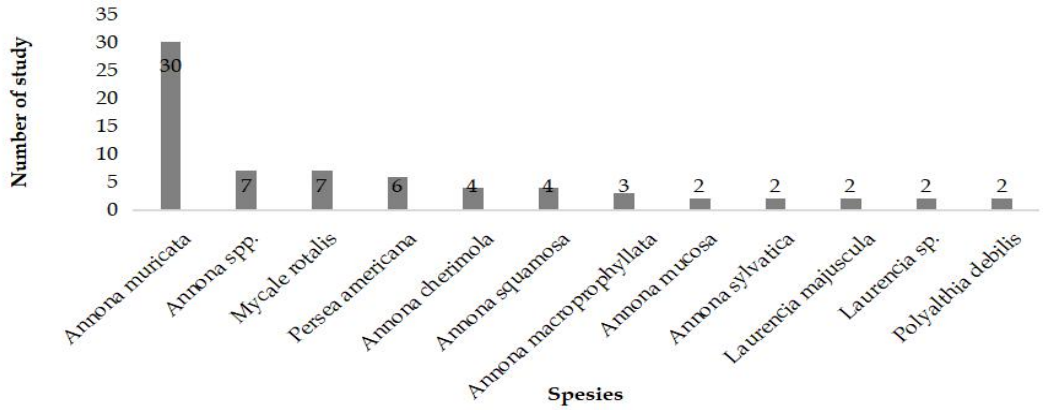

Figure 3. Total number of species containing acetogenins.

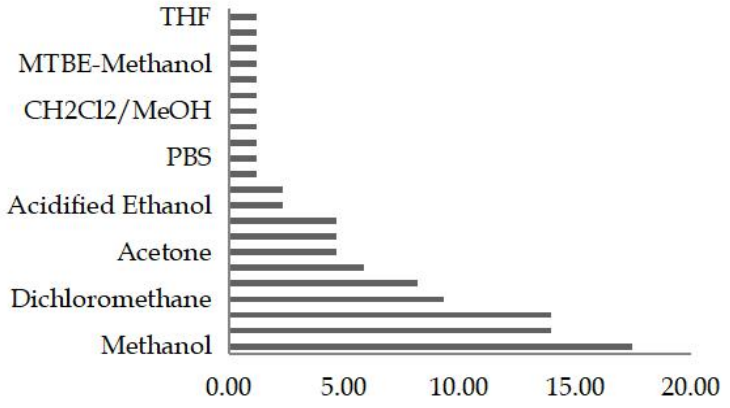

Figure 4. Percentage of solvent types for extracting acetogenin.

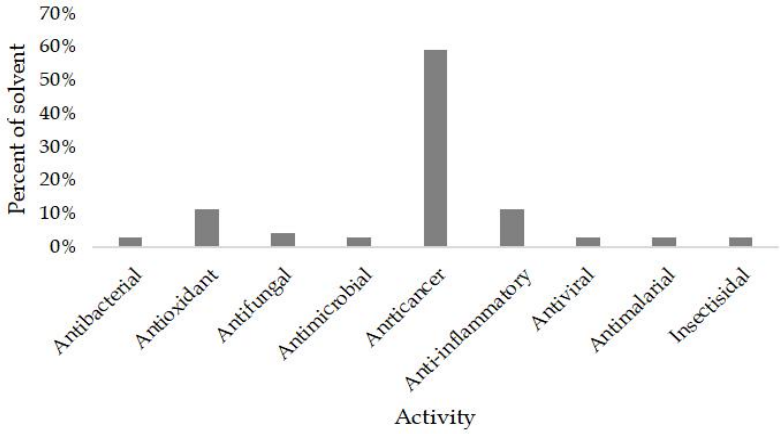

Figure 5. Percentage of solvent types for extracting acetogenin.

degenerative diseases. Although the number of studies on avocado-derived acetogenins is not as extensive as that of Annona (Figure 3), research trends indicate promising prospects for pharmaceutical and functional food applications (Freitas *et al*., 2022).

Another intriguing source of acetogenins comes from marine plants, particularly species

within the Laurencia genus (Gutiérrez-Cepeda *et al*., 2014; Clarke *et al*., 2016; Harizani *et al*., 2022; Kwak *et al*., 2023; Tammam *et al*., 2023) and the marine sponge *Mycale rotalis* (Piccialli, 2017; Capasso *et al*., 2020; Morretta *et al*., 2024). Various Laurencia species, such as *L. obtusa* (Ayyad *et al*., 2011; Esselin *et al*., 2017, 2018; Alarif *et al*., 2019), *L. intricata* (Ishii *et al*., 2019), and *L. majuscula* (Alorfi, Ghandourah & Turki, 2020; Tammam *et al*., 2023), have been studied due to their unique acetogenin structures, which exhibit cytotoxic and antibacterial activities. Research on marine plants has been primarily conducted in countries such as Japan, France, and Italy, which have extensive access to marine biodiversity. The marine sponge Mycale rotalis has also emerged as a subject of interest, as it produces acetogenins with significant anticancer potential (Piccialli, 2017; Capasso *et al*., 2020; Morretta *et al*., 2024).

Beyond these main categories, several other plants have begun to be explored in acetogenin research. For instance, *Miliusa velutina* (Wongsa *et al*., 2017) and *Fragaria spp*. (strawberry) (Hemmati *et al*., 2020; El- Feky & El-Rashedy, 2023) have been investigated for their bioactive compound content, although the number of studies remains limited. This suggests that acetogenin research is not confined solely to plants from the Annonaceae or Lauraceae families but is also expanding toward more diverse sources (Feng *et al*., 2022; Freitas *et al*., 2022).

From this analysis, it can be concluded that acetogenin research is still predominantly centered around plants from the Annona genus, particularly A. muricata, which remains the primary focus of various pharmacological studies. However, the exploration of alternative sources, such as avocado, Laurencia algae, and the marine sponge *Mycale rotalis*, indicates that acetogenins can be found across various plant groups and marine organisms. This trend suggests that future acetogenin research is likely to expand toward exploring novel sources and applications in pharmaceutical and health technology fields (Piccialli, 2017; Capasso *et al*., 2020; Morretta *et al*., 2024).

Extraction, Isolation, and Synthesis of Acetogenins

The extraction and isolation of acetogenins from natural sources, as well as their chemical synthesis, have been extensively studied to optimize yield, purity, and pharmacological efficacy. Traditionally, conventional solvent extraction methods such as maceration and percolation using ethanol, methanol, dichloromethane, and hexane have been employed to obtain crude extracts from *Annona* species and other acetogenin-rich plants (Sousa *et al*., 2023). However, these methods often suffer from low efficiency and long processing times (Brechú-Franco *et al*., 2016).

To improve extraction efficiency, modern technology-based methods such as ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) have been developed. UAE enhances solvent penetration and cell wall disruption, leading to higher acetogenin yields, whereas MAE accelerates extraction through thermal and non-thermal effects, improving efficiency and reducing solvent consumption (Firdausiah *et al*., 2022). Additionally, high-pressure extraction techniques have been introduced to further enhance bioactive compound recovery.

Following extraction, isolation and purification are crucial for obtaining bioactive acetogenins. Chromatographic techniques such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and column chromatography are commonly employed to separate acetogenins from crude extracts. Further structural characterization is conducted using nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) to confirm purity and identity (Crespo *et al*., 2019).

Beyond natural extraction, chemical synthesis and structural modification have emerged as alternative approaches to enhance acetogenin bioavailability and therapeutic efficacy. Total synthesis techniques involve constructing acetogenins from basic chemical precursors, while semi-synthetic modifications improve solubility and target selectivity (Shi *et al*., 2020). Additionally,

Table 1. Biological activities of acetogenins, alkaloids, and related natural compounds: cytotoxicity, antimicrobial, and therapeutic applications.

Isolate	Activities	References
Acetogenins	Inhibition of Bcl-2 proteins	(Antony & Vijayan, 2016)
Acetogenins	Cytotoxicity against glioblastoma	(Sousa *et al*., 2023)
Acetogenins	Improved antitumor efficacy	(Hong *et al*., 2016)
Acetogenins	Cytotoxicity against breast cancer	(Hadisaputri *et al*., 2021)
Acetogenins	Histochemical detection of bioactive compounds	(Laguna Hernández *et al*., 2015)
Acetogenins	Bioinsecticide compatibility with fungi	(Ribeiro *et al*., 2014)
Acetogenins	Enhanced drug delivery for anticancer treatment	(Artanti *et al*., 2020)
Acetogenins	Insecticidal activity	(Firdausiah *et al*., 2022)
Acetogenins	Anti-BPH, antioxidant	(Ogbu *et al*., 2020)
Acetogenins	Anti-glioma	(Ao *et al*., in press)
Acetogenins	Cytotoxicity against breast cancer	(Hadisaputri *et al*., 2021)
Acetogenins, Alkaloids	Anticancer, apoptosis induction	(Chamcheu *et al*., 2018)
Acetogenins, Alkaloids	Histochemical detection of bioactive compounds	(Brechú-Franco *et al*., 2016)
Acetogenins, Alkaloids	Antiproliferative, anticancer activity	(Suresh *et al*., 2011)
Acetogenins, Alkaloids	Inhibition of colon cancer cell migration	(Astuti *et al*., 2021)
Acetogenins, Alkaloids, Flavonoids	Renoprotective, antioxidant, anti-inflammatory	(Zeweil *et al*., 2024)
Acetogenins, Flavonoids, Alkaloids	Cytotoxicity, pro-apoptotic gene modulation	(Abdallah *et al*., 2024)
Acetogenins, Sesquiterpenes	Cytotoxicity against colon, prostate, liver cancer cells	(Alorfi *et al*., 2020)
Acetogenins, Sesquiterpenes	Anti-inflammatory activity	(Tammam *et al*., 2023)
AcO-avocadene, AcO-persenone C	Kemungkinan berperan dalam metabolisme energi dan sinyal seluler	(Colin-Oviedo *et al*., 2022)
Aliphatic Acetogenins	Bioactive lipid metabolism in fruit ripening	(Rodríguez-López *et al*., 2017)
Annonaceous acetogenins	Inhibition of gastric cancer growth	(Li *et al*., 2017)
Annonaceous acetogenins	Antitumor efficacy	(Hong *et al*., 2017)
Annonaceous acetogenins	Antitumor efficacy	(Li *et al*., 2018)
Annonacin	Cancer cell death via NKA and SERCA inhibition	(Yiallouris *et al*., 2018)
Annonacin	Insecticidal activity	(Rodrigues *et al*., 2019)
Annonacin	Cancer pathway modulation	(Md Roduan *et al*., 2019)

nanoparticle-based drug formulations, including liposomal encapsulation and polymer-based nanosuspension systems, have been developed to overcome bioavailability challenges and enhance therapeutic performance (Lü *et al*., 2010).

Despite advancements in extraction, isolation, and synthesis, challenges remain, including low water solubility, potential toxicity, and scalability of production. Future research should focus on optimizing eco-friendly extraction techniques, refining synthetic derivatives, and enhancing drug

delivery systems to fully realize the therapeutic potential of acetogenins in pharmaceutical applications.

Correlation Between Extraction Methods, Isolated Compounds, and Acetogenin Bioactivity

The extraction methods used for acetogenins significantly influence the type and purity of secondary metabolites obtained, which in turn affect their pharmacological activities. Solvent polarity plays a crucial role in isolating specific bioactive compounds. Polar solvents such as ethanol and methanol are highly effective for extracting acetogenins, flavonoids, and alkaloids, while semi-polar solvents like dichloromethane and ethyl acetate are preferred for separating structurally complex sesquiterpenes and halogenated acetogenins (Figure 4). Non-polar solvents, including hexane and petroleum ether, are commonly used for extracting lipophilic acetogenins with high cytotoxic activity (Hernández-Fuentes *et al*., 2019; Sousa *et al*., 2023).

The isolates obtained from these extractions include annonacin, squamocin, annonacinone, and persediene, which exhibit strong anticancer properties by inhibiting mitochondrial function and inducing apoptosis (Crespo *et al*., 2019). In contrast, dichloromethane-extracted sesquiterpenes and polybrominated acetogenins demonstrate potent antimicrobial and anti-inflammatory effects (Rodríguez-Sánchez *et al*., 2019). Advanced purification techniques such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) are essential for separating these metabolites and ensuring compound specificity.

To enhance the pharmacological efficacy of acetogenins, modern formulations such as gold-acetogenin nanosystems and self-micro emulsifying drug delivery systems (SMEDDS) have been developed to improve bioavailability and stability in biological environments (Shi *et al*., 2020). Additionally, structural modifications, including glycosylation and nanoparticle conjugation, have been employed to increase solubility and selectivity in cancer therapy (Hong *et al*., 2016).

Understanding the relationship between extraction methods, isolated secondary metabolites, and their pharmacological properties is crucial for optimizing drug development. Future studies should focus on refining eco-friendly solvent extraction, improving synthetic modifications, and integrating nanotechnology-based formulations to maximize the therapeutic potential of acetogenins.

Distribution and Pharmacological Significance of Secondary Metabolites in Acetogenin Research

The secondary metabolites derived from acetogenin-rich plants exhibit diverse pharmacological activities, including anticancer, antioxidant, anti-inflammatory, and antimicrobial effects. Among the identified metabolites, acetogenins constitute the most dominant group, appearing in approximately 55% of studies. Key bioactive acetogenins such as annonacin, squamocin, bullatacin, and asimicin are known for their potent cytotoxicity, primarily targeting mitochondrial function and inducing apoptosis in cancer cells (Ferreira *et al*., 2023).

In addition to acetogenins, flavonoids account for approximately 20% of reported secondary metabolites. Compounds such as rutin, naringenin, and quercetin, commonly found in *Annona muricata* and *Persea americana*, exhibit strong antioxidant and anti-inflammatory properties, contributing to cellular protection against oxidative stress (Hassan *et al*., 2022). Meanwhile, alkaloids, constituting 12% of identified compounds, including cherimolin-1, molvizarin, and goniothalamin, have demonstrated antimicrobial and cytotoxic effects, although further research is required to fully understand their mechanisms (Hernández-Fuentes *et al*., 2019).

Other secondary metabolites include terpenoids (8%), primarily found in marine algae and sponges, with antibacterial and antifouling activities. Phenolic compounds and tannins (5%) have also been detected in *Annona muricata* and *Persea americana*, showing potential for anti-inflammatory applications (Esselin *et al*., 2018;

Capasso *et al*., 2023). The variation in metabolite distribution highlights the importance of optimized extraction techniques to selectively isolate pharmacologically relevant compounds. Future studies should focus on enhancing solvent selection, structural modifications, and bioavailability strategies, particularly through nanoparticle-based drug delivery systems, to maximize the therapeutic potential of these natural compounds.

Table 1. Biological activities of acetogenins… (continued).

Isolate	Activities	References
Annonacin	Genotoxicity, anticancer potential	(Ferreira *et al*., 2023)
Annonacin	Nutraceutical potential	(Virgen-Ceceña *et al*., 2019)
Annonacin	Cancer cell death via NKA and SERCA inhibition	(Yiallouris *et al*., 2018)
Annonacin, Alkaloids	Identification of bioactive compounds	(Al Kazman *et al*., 2023)
Annonacin, Annonacinone	Apoptosis and anticlonogenic activity	(Webb *et al*., 2024)
Annonacin, Cherimolin-1, Molvizarin	Enhanced bioavailability of acetogenins	(Teresa Gutiérrez *et al*., 2020)
Annonacin, Flavonoids	Antioxidant, Antiproliferative	(Carvalho *et al*., 2022)
Annonacin, Linoleic acid, Oleic acid	Antioxidant, non-toxic	(Pinto *et al*., 2018)
Annopurpuricins A–E	Mitochondrial inhibition, Cytotoxicity	(Hernández-Fuentes *et al*., 2019)
Avocado seed acetogenins	Antifungal, antioxidant properties	(Echenique-Martínez *et al*., 2023)
Bicyclic lactones, Dimeric styrylpyrones	Antimalarial, Cytotoxicity against cancer cells	(Wongsa *et al*., 2017)
Bisabolane sesquiterpenes, Acetogenins	Cytotoxic, bioactivity evaluation	(Liang *et al*., 2012)
Bis-tetrahydropyran analogs	Trypanocidal activity	(Tulloch *et al*., 2017)
Bromoallene acetogenins	Bioactivity assessment	(Esselin *et al*., 2018)
Bromoallene compounds	Potential anticancer activity	(Kamada & Vairappan, 2012)
C12-acetogenins	Anti-inflammatory	(Alarif *et al*., 2019)
C15-acetogenins	Apoptosis induction	(Ayyad *et al*., 2011)
C15-acetogenins	Cytotoxicity	(Bawakid *et al*., 2017)
Chitosan	Biopolymer extraction	(Kimi & Hamdi, 2023)
Cyclocolorenone	Insect repellent activity	(Ishii *et al*., 2019)
Debilisone E	Antimicrobial, cytotoxic effects	(Boonpangrak *et al*., 2015)
Derivatif glikosilasi	Sitotoksik	(Shi *et al*., 2020)
DUPA-konjugat	Sitotoksik	(Periche *et al*., 2023)
Epoxyobtusallene derivatives	Chemical synthesis studies	(Clarke *et al*., 2016)
Ethynyl oxirane acetogenins	Antiproliferative activity	(Morales-Amador *et al*., 2018)
Fl**avonoid**s, Acetogenins	Anti-inflammatory and anti-allergic effects	(Andrade-Silva *et al*., 2020)
Gold-acetogenin nanosystem	Anti-inflammatory, Anticancer	(González-Reyna *et al*., 2024)

Classification of Acetogenins: Structural Variations and Pharmacological Activities

Acetogenins, a diverse class of polyketides primarily found in the Annonaceae family, can be categorized into distinct structural groups, each exhibiting unique pharmacological properties. The most extensively studied category is tetrahydrofuran (THF) acetogenins, known for their potent anticancer activity. Compounds such as annonacin, squamocin, bullatacin, and asimicin exert cytotoxic effects by inhibiting mitochondrial complex I, leading to ATP depletion and apoptosis in cancer cells. Among these, bullatacin has shown cytotoxic potency up to 100 times stronger than some conventional chemotherapy agents (Capasso *et al*., 2023).

Table 1. Biological activities of acetogenins… (*continued*).

Isolate	Activities	References
Goniothalamin, Aristolactam BII	Cytotoxic against cancer cell lines	(Duc *et al*., 2016)
Katsuurallene	Bioactivity analysis	(Minamida *et al*., 2022)
Laherradurin	Antitumor activity	(Rendón-Barrón *et al*., 2024)
Laherradurin	Antitumor activity	(Rendón-Barrón *et al*., 2024)
Laktone asetat	Antiproliferatif	(Capasso *et al*., 2023)
Marilzafurollenes	Stereochemical analysis of bioactive molecules	(Gutiérrez-Cepeda *et al*., 2014)
Mycalin A	Proteomics study of anticancer compounds	(Morretta *et al*., 2024)
Mycalin A and its derivatives	Cytotoxicity against melanoma and cervical cancer	(Capasso *et al*., 2020)
Omaezol, Intricatriol	Antifouling activity	(Oguri *et al*., 2017)
Persediene (Acetogenin)	Antioxidant, anticancer, antiarthritic	(Hassan *et al*., 2022)
Persenone A, Persin	Antimicrobial, safe for human consumption	(Rodríguez-Sánchez *et al*., 2019)
Phenolic acids, phenols, resorcinols	Chemotaxonomy	(Brkljača, Göker & Urban, 2015)
Polybrominated Acetogenins	Potential anticancer activity	(Piccialli, 2017)
Polycyclic aromatic alkaloids	Potential anticancer activity	(Jourjine *et al*., 2022)
Pseudoannonacin	Antifungal activity	(López-Romero *et al*., 2022)
Pyranicin, Pyragonicin	Penghambat DNA polimerase, topoisomerase, sitotoksik	(Murata *et al*., 2019)
Rutin, Gallic acid, Eugenol	Antioxidant, antiviral, antihemolytic	(Balderrama-Carmona *et al*., 2020)
Sagonenyne	Cytotoxic activity against leukemia cells	(Esselin *et al*., 2017)
Sawtehtetronenin	Cytotoxicity against cancer cells	(Thiplueang *et al*., 2014)
Silver nanoparticles	Anticancer, antibacterial, antifungal	(Mokhtar *et al*., 2022)
Squamocin	Cytotoxic against mosquito larvae	(Da Silva Costa *et al*., 2016)
Squamocin	Histone modification, apoptosis induction	(Lee *et al*., 2011)
Squamocin	Insecticidal activity	(Rodrigues *et al*., 2019)
Squamocin	Insecticidal activity	(Costa *et al*., 2014)
Squamocin, Alkaloids	Cytotoxicity against leukemia cells	(Parra *et al*., 2021)
Various C15-acetogenins	Antibacterial activity	(Harizani *et al*., 2022)
Various plant extracts	Chemopreventive against colorectal cancer	(Iwo *et al*., 2023)

A second major category, non-THF acetogenins, lacks the tetrahydrofuran ring but retains strong anticancer and antimicrobial properties. Pyranicin and pyragonicin inhibit DNA polymerase and topoisomerase, disrupting cancer cell replication. Additionally, persin and persenone A, derived from *Persea americana* (avocado), exhibit antioxidant and selective cytotoxicity against breast cancer cells (Hernández-Fuentes *et al*., 2019).

Another subclass includes brominated/ halogenated acetogenins, characterized by the presence of halogen atoms, which enhance cytotoxic and antibacterial activities. Bromoallenes, found in *Laurencia* species, exhibit potent anticancer and antioxidant effects, while polybrominated acetogenins from marine sponges demonstrate high cytotoxicity against melanoma and cervical cancer cells (Kamada & Vairappan, 2012; Piccialli, 2017).

Recent advancements in nanoparticle formulations have led to the development of liposomal acetogenins and glycosylated derivatives, aimed at improving solubility, selectivity, and bioavailability. Liposomal acetogenins have shown enhanced penetration into glioblastoma and colorectal tumors, increasing therapeutic efficacy. Meanwhile, glycosylated derivatives have been designed to selectively target prostate cancer cells by improving interactions with prostate-specific membrane antigens (PSMA (Shi *et al*., 2020).

The structural diversity of acetogenins significantly influences their mechanisms of action and therapeutic potential (Table 1). Future research should prioritize structural modifications, synthetic derivatives, and advanced drug delivery systems to optimize their clinical applications.

Pharmacological Activities of Acetogenins: Mechanisms and Therapeutic Potential

Acetogenins, a class of bioactive polyketides primarily found in the Annonaceae family, exhibit a broad range of pharmacological activities, including anticancer, anti-inflammatory, antioxidant, and antimicrobial effects (Figure 5). Their diverse mechanisms of action make them promising candidates for drug development in oncology, infectious diseases, and metabolic disorders (Ferreira *et al*., 2023).

1. Anticancer Activity

Acetogenins have demonstrated potent cytotoxicity against various cancer cell lines, including glioblastoma, breast cancer, melanoma, cervical cancer, and colorectal cancer. Their primary mechanism involves mitochondrial complex I inhibition, leading to ATP depletion and apoptosis induction. Compounds such as annonacin and squamocin suppress cancer cell proliferation by modulating key apoptosis regulators, including Bcl-2 and caspase pathways. Additionally, some acetogenins inhibit cancer cell migration and metastasis, making them promising candidates for targeting aggressive tumors (Liaw *et al*., 2016; Lee, Lee & Kim, 2020).

2. Anti-Inflammatory and Antioxidant Activity

Acetogenins exhibit anti-inflammatory properties by downregulating pro-inflammatory cytokines (TNF-α, IL-6) and inhibiting oxidative stress pathways. Their ability to scavenge free radicals and protect against oxidative damage suggests potential therapeutic applications in neurodegenerative diseases such as Alzheimer's and Parkinson's. Studies have also shown renoprotective effects, indicating that acetogenins may mitigate kidney damage in diabetic and hypertensive patients (Liaw *et al*., 2016).

3. Antimicrobial and Insecticidal Activity

Several acetogenins have exhibited antibacterial, antifungal, and antiviral activities, primarily by disrupting microbial cell membranes and inhibiting essential metabolic enzymes. Certain derivatives, such as persediene and debilisone E, demonstrate significant cytotoxic and antimicrobial properties. Additionally, acetogenins have been explored as natural bioinsecticides, showing high efficacy against mosquito larvae and agricultural pests (Rupprecht & Mclaughlin, 1990).

4. Modulation of Energy Metabolism and Cellular Signaling

Emerging research indicates that acetogenins influence energy metabolism pathways, making

them potential candidates for metabolic disorders such as diabetes and obesity. Studies suggest that certain acetogenins enhance insulin sensitivity and reduce lipid accumulation, highlighting their potential in diabetes management. Additionally, compounds such as AcO-avocadene and AcO-persenone C play a role in cellular energy regulation, further expanding their therapeutic applications (Gajalakshmi, Vijayalakshmi & Devi Rajeswari, 2012; Jacobo-Herrera *et al*., 2019).

Future Directions

Despite their promising pharmacological effects, clinical translation of acetogenins remains limited due to challenges such as poor water solubility, potential neurotoxicity, and limited bioavailability. Advances in nanoparticle-based drug delivery systems and structural modifications have been explored to overcome these limitations and enhance therapeutic efficacy (Chang *et al*., 2021). Future research should focus on optimizing formulation techniques, conducting in-depth clinical trials, and exploring novel acetogenin derivatives for targeted therapy.

CONCLUSION

Acetogenins have emerged as a promising class of bioactive natural compounds, particularly in oncology, antimicrobial therapy, and metabolic disorders. This review highlights their diverse pharmacological activities, with strong evidence supporting their cytotoxic, anti-inflammatory, antioxidant, and antimicrobial properties. Their primary mechanism of action, mitochondrial complex I inhibition and apoptosis induction, makes them particularly effective against various cancers, including breast, colorectal, glioblastoma, and leukemia. Additionally, advancements in extraction techniques, nanoparticle-based drug delivery, and structural modifications have significantly improved their therapeutic potential.

Despite these promising findings, several challenges remain, including low bioavailability, potential neurotoxicity, and the need for clinical validation. Future research should focus on developing targeted drug formulations, optimizing synthetic derivatives, and conducting extensive in vivo and clinical studies to enhance efficacy and safety. By integrating advanced drug delivery systems and interdisciplinary collaborations, acetogenins hold immense potential as next-generation natural therapeutics in cancer treatment and beyond.

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