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Pharmacological Evaluation of Atranorin: A Comprehensive Study on its Biological Activities

Tiruveedhula Somasekhar[1]*, Narayana Rao Gundoju[2], Boddu Rama Krishna[3] and Waill Elkhateeb[4]

[1]Department of Humanities & Sciences, Vidya Jyothi Institute of Technology, Aziznagar Gate, Chilkur Balaji Road, Himayat Sagar Rd, Hyderabad, Telangana 500075, India
[2]Department of Chemistry, Maharajah's College autonomous, Vizianagaram, Andhra Pradesh 535002, India
[3]Department of Chemistry, S.V.R.M College Nagaram, Guntur-522 268, Andhra Pradesh, India
[4]Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Division, National Research Centre, Dokki, Giza 12622, Egypt

Abstract

Lichens are a rich source of diverse secondary metabolites, with depsides playing a crucial role in their biological properties. Atranorin, a prominent depside, has been widely studied due to its significant pharmacological effects. This review explores the biosynthesis of atranorin, elucidates its molecular structure, and presents insights from docking studies that reveal its interactions with key biological targets. Furthermore, the diverse biological effects of atranorin including anti-cancer, anti-inflammatory, antiviral, antioxidant, and antifungal activities are discussed. These findings highlight atranorin's broad therapeutic potential, making it a promising candidate for drug development.

Introduction

Lichens are complex microbial communities, primarily defined by a symbiotic relationship between a fungal partner (mycobiont) and a photosynthetic organism (photobiont), typically a green alga or cyanobacterium [1,2]. Lichenized fungi produce various secondary metabolites, which are biosynthesized via three principal pathways: the shikimate pathway, the mevalonate pathway, and the polyketide pathway [3]. To date, well over 1,000 lichen secondary metabolites have been reported, most of which are phenolic polyketides found exclusively in lichens. The genesis of aromatic lichen metabolites transpires during the acetate-poly malonate biosynthetic pathway, facilitated by the catalytic action of Polyketide Synthase (PKS) enzymes. Most of these secondary metabolites are low molecular weight phenolic compounds such as depsidone, quinones, xanthones, dibenzofurans and flavones [4-8].

Atranorin is a phenolic aromatic compound classified as a depside, found in various lichen families, including *Parmotrema melanothrix* [1], *Parmotrema rampoddense* [9], *Parmotrema tinctorum* [10], as well as in

***Corresponding author(s)**

Tiruveedhula Somasekhar, Department of Humanities & Sciences, Vidya Jyothi Institute of Technology, Aziznagar Gate, Chilkur Balaji Road, Himayat Sagar Rd, Hyderabad, Telangana 500075, India

Email: sekhar.msc25@gmail.com

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the *Cladoniaceae, Parmeliaceae*, and *Stereocaulaceae* families [11]. Atranorin classified by a fundamental structure of β-orcinol units connected through ester linkages (Figure 1), exhibits diverse range of biological activities including antimicrobial, anticancer, anti-inflammatory, antinociceptive, antiviral, wound-healing, and photoprotective properties [12-14].

Atranorin, with notable physicochemical properties such as 27 heavy atoms, 6 rotatable bonds, 8 hydrogen bond acceptors, 3 hydrogen bond donors, a molar refractivity of 95.48, and a topological polar surface area of 130 Å², and showing no violations of Lipinski's rule of five, is well-positioned to interact strongly with cancer-related proteins, demonstrating good druggability [9]. This review delves into the biosynthesis of atranorin and examines its relevance due to its range of biological activities.

Bio-synthesis of atranorin

Atranorin biosynthesis initiates with acetyl-CoA carboxylase catalyzing the conversion of acetyl-CoA to malonyl-CoA via ATP hydrolysis, followed by sequential Claisen decarboxylative condensations with malonyl-CoA to elongate the polyketide chain. The biosynthesis of Atranorin is shown in figure 2.

This pathway incorporates acetyl-CoA and three malonyl-CoA molecules to generate the polyketide precursor. Isotopic labeling studies using malonyl-CoA and formic acid elucidated specific integration sites in atranorin. Crucial enzymes in the Polyketide Synthase (PKS) complex include Keto-Synthase (KS), Acyltransferase (AT), and Acyl Carrier Protein (ACP), augmented by optional domains such as Ketoreductase (KR), Dehydratase (DH), Enoylreductase (ER), and Methyltransferases (MT) that diversify the polyketide chain. Post-elongation, Claisen condensation yields phenolic acids with methyl substituents, followed by orcinolic cyclization to form aromatic acids endowed with carboxyl, hydroxyl, and methyl functionalities. Specific modifications, including the integration of labelled formic acid into the β-methyl and aldehyde groups of atranorin, are mediated by intrinsic PKS

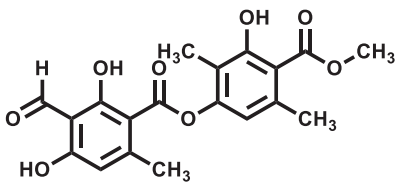

Figure 1 Structure of the Atranorin.

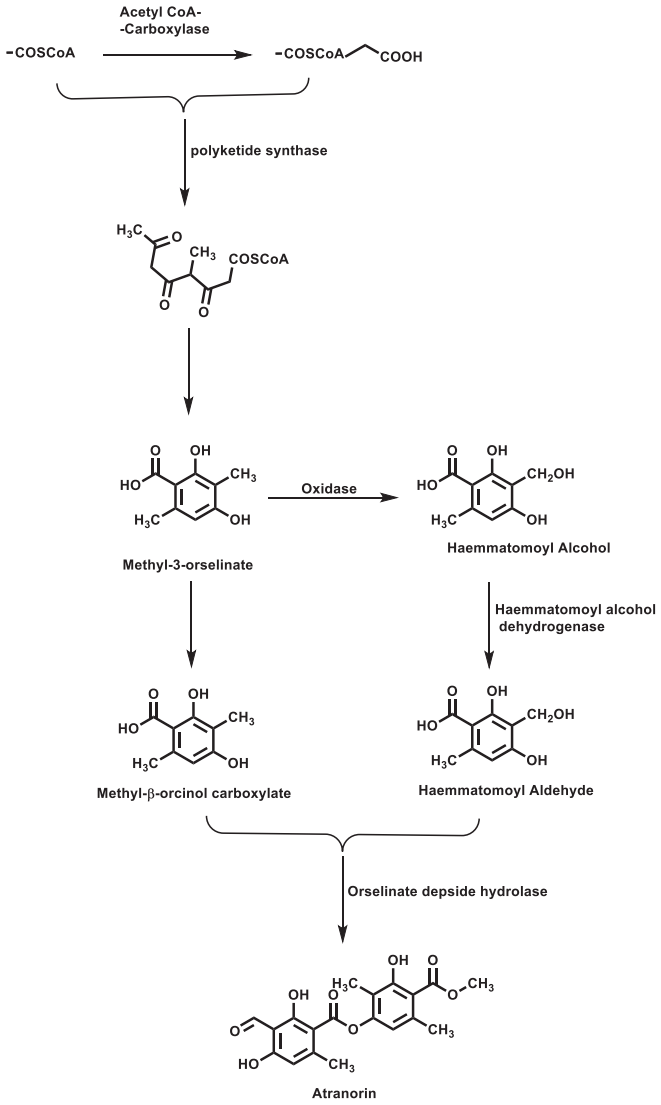

Figure 2 Biosynthesis of Atranorin.

enzymes, notably MT subunits, which facilitate methylation during chain elongation. Consequently, atranorin is synthesized through the polyketide pathway involving key PKS enzymes, precise cyclization mechanisms, and tailored functional group modifications [15].

Anti-cancer

Phytochemicals with lower binding energies (measured in kcal/mol), usually have higher affinity and are better drug candidates. Docking studies of atranorin have shown it to have more favourable binding sites with various cancer-causing proteins. Molecular docking of atranorin showed binding energies of -7.4 kcal/mol for Bcl-2, -7.2 kcal/mol for Bcl-XL, -7.1 kcal/mol for CCNA 1, -8.8 kcal/mol for CCND 1, -7.1 kcal/mol for CCNE 1, -8.2 kcal/mol for

VEGFR 1, and -7.5 kcal/mol for VEGFR 2. Atranorin had the lowest binding energies with Bcl-2 and Bcl-XL, suggesting it can effectively block anti-apoptotic proteins and promote apoptosis. Its strong binding to CCND 1 also indicates a potential for cell cycle arrest at the G1 phase [11]. A. Harikrishnan, et al. [16] investigated the effects of atranorin on breast cancer-related proteins such as AKT (P31749), BCL-2 (P10415), BAX (Q07812), BCL-W (Q92843), and BCL-XL (CAA80661.1). They found that atranorin binds to the allosteric sites of these proteins with an inhibitory concentration of 2.61 µM, 97.8 µM, 105.6 µM, 726.9 µM, and 159.20 µM, respectively. Cytotoxicity studies demonstrated that ATR selectively inhibited triple-negative breast cancer cells (MDA-MB-231) at a concentration of 5.36±0.85 µM and triple-positive breast cancer cells (MCF-7) at a concentration of 7.55 ± 1.2 µM. Interestingly, normal HEK-293 cells, which lack the expression of the specific proteins targeted by ATR, exhibited no significant effects from the treatment. Atranorin does not exhibit cytotoxic activity at 5 µg/mL concentrations. However, at this concentration, it significantly inhibits A549 cell motility, with a 46% reduction in migration and a 33% reduction in invasion. These results demonstrate that atranorin possesses potential inhibitory activity against A549 (lung cancer) cell motility. The expression of c-myc, cyclin-D1, and CD44 is regulated by the β-catenin/TCF4 and LEF1 complex. Atranorin treatment in lung cancer cells significantly decreased the relative expression levels of CD44, cyclin-D1, and c-myc [17]. KITENIN enhances the tumorigenic capabilities of cancers, with Epidermal Growth Factor (EGF) promoting KITENIN-driven activation of AP-1[18]. Atranorin impeded A549 cell motility, in part, by attenuating KITENIN-mediated AP-1 activity, achieved through the modulation of KITENIN and KAI1 expression in lung cancer cells [17].

Anti-inflammatory

Lichen substances exhibit anti-inflammatory activity, and studies have investigated that nearly 70 of these compounds may have potential against inflammation. DellaGreca M, et al. [4], reported that atranorin, derived from the methanol extract of **Parmotrema hypoleucinum**, exhibited significant anti-inflammatory potential (76%) by reducing Nitric Oxide (NO) levels in Lipopolysaccharide (LPS)-stimulated macrophages. Barrows, et al. [5] isolated both chloroatranorin and atranorin from a hexane extract of **Parmelina saccatilobum** and tested them in a COX-1 and COX-2 enzyme inhibition assay. The results showed that atranorin inhibited COX-1 in a dose-dependent manner. Additionally, the study suggested that atranorin partially inhibits COX-2, while chloroatranorin partially inhibits COX-1. Kumar and Müller investigated the anti-inflammatory effects of atranorin in both *In vitro* studies on leukotriene B4 synthesis in polymorphonuclear leukocytes. Atranorin exhibited strong inhibition of LTB4 biosynthesis, achieving an IC_{50} value of 6.0 ± 0.4 µM. For comparison, the reference compounds nordihydroguaiaretic acid and anthralin had IC_{50} values of 0.4 ± 0.21 µM and 37 ± 4.6 µM, respectively [6]. The potential anti-inflammatory effects of atranorin atranorin at doses of 100 and 200 mg/kg were evaluated in a carrageenan-induced paw edema model in Wistar rats. The findings revealed that atranorin significantly reduced paw edema and leukocyte migration, indicating strong anti-inflammatory activity. Additionally, there were no signs of significant acute or subchronic toxicity, nor any cytotoxic effects on other organs [7].

Anti-viral

Lichens have proven to be a promising source of antiviral drugs. Numerous studies have demonstrated the antiviral properties of lichens. Wei, et al. [19] found that atranorin effectively protects SNB-19 cells from Zika Virus (ZIKV) infection. This protective effect is evidenced by a reduction in viral protein expression and a decrease in progeny virus production. Atranorin also mitigates the activation of the Interferon (IFN) signaling pathway and the subsequent inflammatory response induced by ZIKV infection. Results from the time-of-addition assay suggest that atranorin primarily interferes with the viral entry process.

Jacques Le Seyec conducted a phytochemical study of **Stereocaulon evolutum**, focusing on the isolation of atranorin derivatives. Atranorin, the primary metabolite of this lichen, has been shown to interfere with the lifecycle of Hepatitis C Virus (HCV). Most of these compounds exhibited activity against HCV, with half-maximal inhibitory concentrations ranging from 10 to 70 µM. Specifically, atranorin, which contains an aldehyde group at C-3, was effective in inhibiting only viral entry [20].

Antioxidant

Antioxidant activity of Atranorin (AT) is crucial for understanding its role in systematics and phylogeny. In general, antioxidant activity has primarily been assessed using various chemical *In*

vitro assays, such as free radical scavenging, reducing power, and lipid peroxidation inhibition. The Total Reactive Antioxidant Potential (TRAP) assay is used to measure the antioxidant capacity of samples *In vitro* [21]. This method relies on the suppression of luminous-enhanced Chemiluminescence (CL), which originates from the thermolysis of 2,2'-Azo-Bis(2-Amidinopropane) dihydrochloride (AAPH) as a source of free radicals [22]. The study noted that atranorin exhibited a strong radical scavenging effect, with IC_{50} values of 39.31 µM [23]. The antioxidant and free radical scavenging capabilities of AT were assessed using the TRAP and TAR assays [24]. These methods are commonly used to determine the non-enzymatic antioxidant potential of isolated substances or mixtures. In the TRAP assay, AT demonstrated dose-dependent antioxidant activity [24]. The TAR analysis revealed that AT significantly scavenges free radicals at a dose of 100 µg/ml [25]. These findings suggest that AT functions as a general antioxidant in systems that generate free radicals, implying its potential to protect against oxidative damage caused by metabolic stress or xenobiotics. Atranorin exhibited peroxyl radical scavenging activity at concentrations ranging from 0.1 to 100 µg/mL in the TRAP/TAR assays [26]. It also displayed significant superoxide dismutase-like activity, highlighting its antioxidant potential against superoxide radicals. However, in a lipid-rich system, atranorin demonstrated a pro-oxidant capacity by increasing TBARS formation induced by the thermolysis of 2,2'-Azo-Bis-(2-Amidinopropane) dihydrochloride (AAPH) incubation. In assays evaluating its antioxidant potential against NO and H_2O_2, atranorin was found to enhance the production of these species, acting as a pro-oxidant molecule, but only at higher concentrations. Hydrogen peroxide is known to cause cell death through oxidative stress-dependent necrosis and apoptosis, resulting from extensive oxidative damage to DNA, lipids, and proteins. The observed pro-oxidative effects are likely related to the concentration range tested, as lower doses (100-250 µM) have been shown to reduce H_2O_2/$FeCl_2$ and inhibit lipid peroxidation (LPO), thus protecting against oxidative damage by inhibiting both Reactive Oxygen Species (ROS) and free radicals [28]. These findings are supported by the studies of Papadopoulou, et al. [27] and Kosanić, et al. [29], who also reported significant antioxidant activity of atranorin (0.012-0.017 mg/mL) in the Co(II)/EDTA-induced luminol plateau chemiluminescence assay and demonstrated very strong antioxidant activity in the DPPH, SAS, and reducing power assays, respectively [29].

These antioxidant properties may contribute to its pharmacological effects, including reducing skin damage and modulating the wound healing process [30]. The antioxidant properties of atranorin have been evaluated in various studies. Conducted several free radical inhibition tests, including those for hydroxyl radicals, hydrogen peroxide, superoxide, and nitric oxide. They also performed Total Reactive Antioxidant Potential (TRAP) assays, Total Antioxidant Reactivity (TAR) index measurements, and *In vitro* lipid peroxidation assays. In the TRAP and TAR assays, atranorin showed a dose-dependent antioxidant capacity, with significant effects at concentrations of 100 µg/mL. While it effectively reduced superoxide radical formation, it also led to a marked increase in hydrogen peroxide production *In vitro* and heightened lipid peroxidation induced by the free radical-generating compound AAPH.

Antifungal

Mayurika Goel et.al, isolated and identified Atranorin from *Parmelia reticulata*. Atranorin displayed the highest antifungal activity, inhibiting soilborne pathogenic fungi *Sclerotium rolfsii* by 100%, 89%, and 67% at concentrations of 250, 125, and 62.5 µg/mL, respectively, with an ED_{50} value of 39.70 µg/mL [31]. Xiao-Ning, et al. [32] evaluated the antifungal activity of atranorin against Candida albicans using a TLC bioautographic assay. The minimum inhibitory concentration ranged from 2.0 to 15 micrograms, with miconazole serving as the reference drug

Conclusion

In conclusion, although atranorin has shown promising biological activities, research on this lichen-derived metabolite remains relatively limited. To fully realize its potential, further studies are crucial, particularly those evaluating its efficacy against contemporary diseases such as COVID-19, antimicrobial resistance, cancer, and inflammatory disorders. Given the increasing demand for novel therapeutic agents, more in-depth research into atranorin's mechanisms of action, structure-activity relationships, and pharmacological properties is essential. Expanding clinical evaluations could facilitate the development of new drugs with broad-spectrum therapeutic potential.

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