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# Recent advancements of 'scytonemin' and its potential to sustainable and green world

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## *ABSTRACT*

*Ultraviolet (UV) radiation poses a significant threat to cyanobacteria by inducing cellular damage through photo-oxidation, resulting in the formation of harmful photosensitized proteins and pigments. To thrive in such harsh conditions, certain cyanobacteria have evolved to produce compounds like indole-alkaloid sunscreen and scytonemin within their extracellular sheaths. These compounds offer photoprotection and mitigate oxidative stress. Scytonemin, characterized by its hydrophobic nature and stability, acts as an antioxidant with considerable biotechnological aspects. The presence of a primitive array of ultraviolet-absorbing pigments in phylogenetically ancient cyanobacteria indicates an evolutionary adaptation to UV radiation. Scytonemin synthesis involves biosynthetic precursors tyrosine and tryptophan. Within a cluster of 18 genes (NpR1276 to NpR1259), genes NpR1274 to NpR1271 are pivotal in scytonemin biosynthesis. Understanding scytonemin biosynthesis at the molecular level holds promise for its application in biotechnology. This review aims to summarize scytonemin biosynthetic gene clusters, their transcriptional regulations, evolutionary significance, and biotechnological properties. By advancing our understanding, it seeks to facilitate the screening of appropriate cyanobacteria for the scytonemin synthesis for various applications.*

***Keywords:*** *Biosynthesis, gene cluster, phylogenetically scytonemin, transcriptional regulation.*

## Introduction

Cyanobacteria, the earliest Gram-negative prokaryotes, emerged during the Precambrian era and have pivotal role in oxygen evolution, fostering the development of diverse life forms [1]. However, contemporary challenges such as anthropogenic atmospheric pollutants and ozone depletion have intensified UV radiation reaching Earth's surface, posing significant threats to cyanobacteria. To counteract these challenges, cyanobacteria produce photo-protective compounds, including scytonemin [2-3]. Scytonemin is synthesized within the extracellular polysaccharide sheath of approximately 300 cyanobacterial species was first identified by Nägeli in certain terrestrial cyanobacteria [4]. This matrix comprises heteroglycans, peptides, proteins, DNA, and various secondary metabolites. Dark yellow to brown coloration of the sheath is due to the deposition of this lipid-soluble yellow-brown pigment (Figure 1) [5].

Its protective role against harmful UV irradiation and facilitating adaptation to challenging environments is demonstrated by the experiments conducted in *Nostoc flagelliforme*, found in the upper layers of microbial mat communities exposed to high solar irradiance [6]. It is approximately 5 % of the cellular dry weight of the culture [7]. Extraction methods involve the use of 100 % acetone, with subsequent re-cultivation of *Lyngbya* sp. allowing for extraction after three weeks [8-12].

Research suggests that scytonemin synthesis is influenced by various environmental factors, including hydration periods, nitrogen availability, salt stress, UV radiation (particularly UV-B), high light intensity, and temperature [13-15]. For instance, longer hydration periods between desiccation cycles in *Nostoc punctiforme* promote higher scytonemin synthesis. Conversely, periodic desiccation inhibits scytonemin synthesis in *Chroococcidiopsis*, with nitrogen restriction leading to increased production [16-19]. While the exact mechanism of scytonemin induction remains unclear, it is evident that multiple environmental signals modulate its levels in different cyanobacterial species. Scytonemin serves as a crucial defense mechanism for cyanobacteria against environmental stressors, highlighting its importance in microbial adaptation and survival strategies [20-22].

*Figure 1: Photograph of Lyngbya sp. showing scytonemin in its sheath.*



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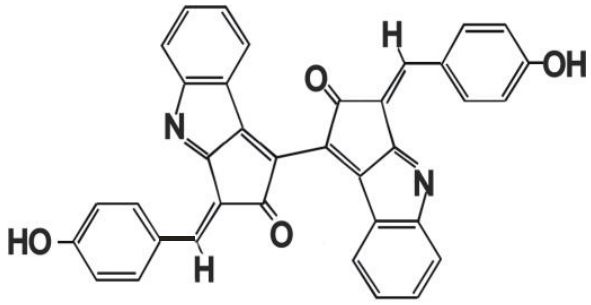
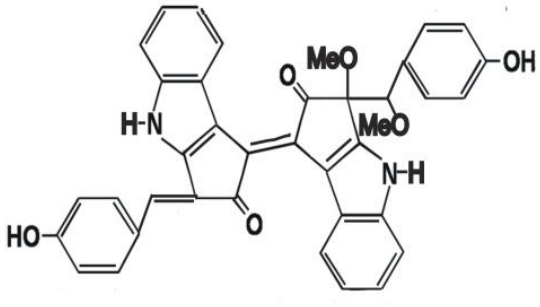
MALDI-TOF MS analysis, demonstrated that scytonemin composed of indolic and phenolic subunits, possesses a molecular mass of 544 Da and its molecular formula is $C_{36}H_{20}N_2O_4$ [23-25]. This analysis revealed characteristics identical to the oxidized state of scytonemin. Its IUPAC name is (3E,3'E)-3,3'-Bis(4-hydroxybenzylidene)-1,1'-bicyclopenta[b]indole-2,2'(3H,3'H)-dione [26-27]. The linkage between the subunits of scytonemin occurs at an olefinic carbon atom, which is a exclusive feature among natural compounds [28-34], defining a novel ring system termed 'the scytonemin skeleton' [35-36].

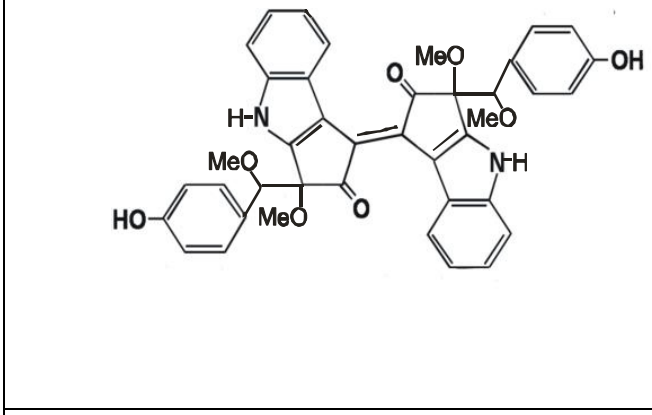
It exists in both oxidized (fuscochlorin, green) and reduced (fuscorhodin, red) forms. Additionally, *Scytonema* sp. has yielded derivatives such as dimethoxyscytonemin, tetramethoxyscytonemin, and scytonin (Figure 2). Purified scytonemin exhibits peak absorption at 380 nm and is identifiable in cyanobacteria via MALDI-TOF MS, with its absorption spectrum covering the UVC-UVB-UVA-violet-blue spectral range [37]. Analysis of scytonemin commonly employs UV-absorbance, HPLC, and Raman spectroscopy techniques, facilitating precise characterization and quantification in various biological contexts and enhancing our understanding of its roles and attributes within cyanobacteria [38-39].



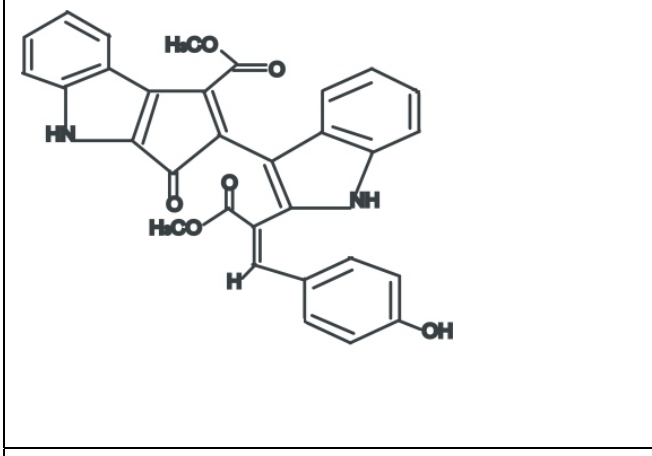

**Scytonemin**




**Dimethoxyscytonemin**




**Tetramethoxyscytonemin**




**Scytonin**

***Figure 2: Chemical structure of scytonemin and their derivatives.***

Scytonemin serves as a protective shield for cyanobacteria against UV radiation, essentially acting as a sunscreen [25]. This protective function extends to cyanobacterial lichens like *Collema, Gonohymenia, Petulla*, etc., shielding them from high radiation levels [32]. Its role as a UV shield was studied in the terrestrial cyanobacterium *Chlorogloeopsis* sp. [33]. *Nostoc punctiforme* cells, remained intact even after 2 months of constant exposure to UV-A radiation, demonstrated the remarkable stability of this metabolite [16]. In *Lyngbya sp. CU2555*, with minimal impact on its absorption properties, it exhibits environmental stability against various stress [34].

Some scientists have reported the preservation of scytonemin in sedimentary lakes [35], while others have noted its abundant preservation in deep sea sediments, indicating its resilience and resistance to degradation during erosion and transport [36]. Consequently, scytonemin stands as a significant biomarker in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paleoclimatological reconstructions and terrestrial extreme environments [37-39].

**Scytonemin biogenesis and its transcriptional regulation**

Scytonemin, a heterocyclic indole-alkaloid compound is synthesized from tryptophan and tyrosine derivatives, both of which absorb UV-B radiation. The genes for scytonemin biosynthesis are present as a single operon, comprising Scy genes (core genes), Ebo genes (responsible for transporting an intermediate product into the periplasm for final assembly), and additional genes involved in precursor synthesis from tryptophan. Within the *N. punctiforme* genome, NpR1276 to NpR1259 genes, have been identified which are associated with scytonemin biosynthesis. Six conserved genes within this cluster, NpR1276 to NpR1271 (ScyA to ScyF), have a substantial role in scytonemin biosynthesis. The process occurs in three modules: Module I (ScyABCDEF) catalyzes the formation and oxidation of the scytonemin monomer, while Module II (NpR1270-NpR1259) translocates the monomer to the periplasm. Module III (EboABCEF) facilitates this translocation process (Figure 3).

ScyA (NpR1276) initiates synthesis by coding for acetolactate synthase, which condenses pyruvate molecules. Oxidative deamination of L-tryptophan, yielding indole-3 pyruvic acid is catalysed by ScyB (NpR1275). Subsequent steps involve cyclization, decarboxylation, and monomer dimerization to form scytonemin (Figure 4). While ScyD and ScyF may not be essential, they likely contribute to scytonemin synthesis. Moreover, NpR1270 (TryP), a copper monooxygenase, is crucial for tyrosine oxidation, a pivotal step in scytonemin biosynthesis. Additionally, genes NpF5232 to NpF5236 are associated with scytonemin biogenesis and are upregulated under UV-A radiation.

Transcriptional studies in *N. punctiforme* reveal that UV-A radiation upregulate scytonemin biosynthesis genes leading to the synthesis of tryptophan and p-hydroxyphenylpyruvate monomers, which undergo processing in the cytoplasm before being transported to the periplasm for further enzymatic reactions, resulting in the formation of the scytonemin (reduced form). Once secreted into the extracellular matrix, scytonemin blocks incoming UV-A radiation, thereby regulating gene expression and halting further scytonemin synthesis. It is suggested that a type IV secretion system is involved in secreting scytonemin to the extracellular matrix. These mechanisms underscore the intricate regulation of scytonemin biosynthesis and its pivotal role in protecting cyanobacteria from UV radiation.

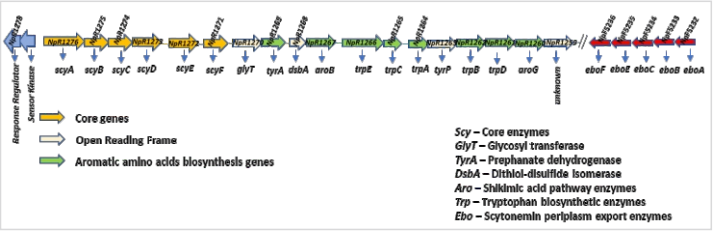


***Figure 3: Genes for scytonemin biosynthesis, periplasmic export, and regulation in cyanobacteria.***

Two-component regulatory system (TCRS), composed of a sensor kinase (histidine kinase) (NpRF1277) and a response regulator (NpRF1278), which is highly conserved lies adjacent to the scytonemin biosynthetic gene cluster (Figure 3). Study demonstrated that a mutant lacking NpRF1278 failed to produce scytonemin under UV-A stress compared to the wild type [55]. NpRF1277 is an HKII-type histidine kinase containing the structural domains of HKII + (PAS)2 PAS/PAC. PAS/PAC domains can bind small molecules, thereby signaling responses to stimuli such as light, oxygen, pH, and salinity. The response regulator NpRF1278 is an RRII featuring an AraC output DNA-binding domain [56]. The expression response of TCRS to light and UV radiation differs from that of cells exposed to oxidative stress, indicating its photosensitivity [57].

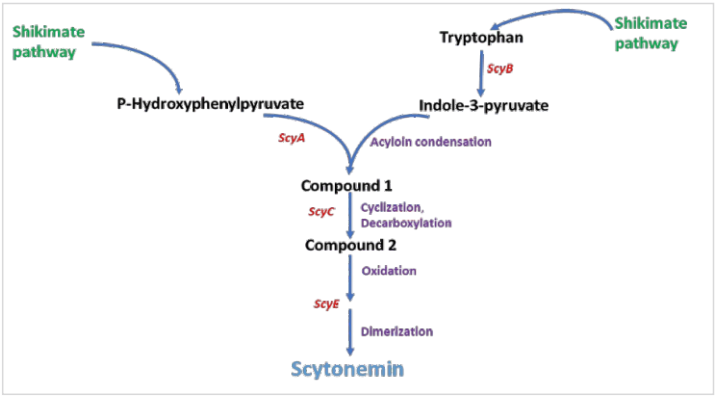


***Figure 4: Scytonemin biosynthesis pathway.***

**Role of scytonemin in evolution**

During the early Proterozoic era, cyanobacterial photosynthesis markedly increased oxygen levels, while UV radiation remained abundant on Earth's surface. There likely existed mechanisms to balance UV radiation and photosynthetically active radiation (PAR), crucial for life's evolution during that period (Figure 5). Early photosynthetic life depended on protective organic molecules in aquatic habitats [58]. UV-screening compounds, evolving during the Precambrian era, provided UV protection, potentially enhancing cyanobacteria's resilience to high radiation [29]. While the chemistry of the first specific UV-absorbing molecules on Archean Earth remains poorly understood, aromatic-containing reaction centres probably served as some of the earliest UV screens, enabling cyanobacteria to harvest light for photosynthesis [59]. The presence of ancient UV-absorbing pigments in modern cyanobacteria, ranging from UVC-absorbing pigments in the Archean eon to pigments absorbing longer UV wavelengths in the Phanerozoic eon, suggests the evolutionary selection of photon dissipation mechanisms for photo-protection throughout life's history [24].

Considerable amounts of scytonemin have been observed in the top deposits of the terrestrial cyanobacterial mats or crusts, offering shield to cells beneath by dissipating UV radiation [19, 60]. The presence of scytonemin in Precambrian era mats with silica, likely provided similar protection in extreme photic environments. Scytonemin's long-term stability [33] is advantageous for understanding life's evolutionary history in paleobotanical studies. It holds substantial role in ecological management, as it often accrues in the upper layers of cyanobacterial mats thriving in intensely sunlight-exposed regions. Scytonemin's evolutionary functions include UV absorption, antioxidant properties, reduced ROS production and thymine dimers, heat dissipation from absorbed UV radiation, and increased soil surface temperature [4, 34, 61, 62]. This contributes to cyanobacteria's high tolerance to desiccation [16] and stabilization of the exopolysaccharide matrix [63]. Scytonemin interacts with the WspA protein (in matrix), enables desiccation resistance in cyanobacteria [64]. It also forms iron-complexes that enable the cyanobacterial survival on rocks [65, 66].


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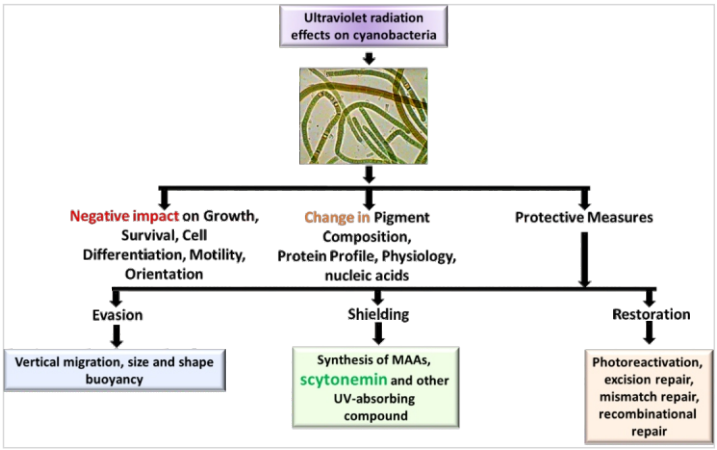


***Figure 5: Stratagems by cyanobacteria to counteract high radiations.***

**Biotechnological potential of scytonemin**

Cyanobacteria offer a promising avenue for biogenesis of fuels, chemicals, medicines, plant secondary metabolites etc. [67-71]. They serve as a valuable source of biofuels [72]. Ultraviolet (UV) radiation poses risks such as sunburn, premature skin aging, and skin cancer, including malignant melanoma, due to repeated exposure to sunlight's high radiations [73]. To counteract the detrimental effects of high radiations, cyanobacteria synthesize scytonemin, that acts as a natural substitute to synthetic UV filters to safeguard them [74]. Scytonemin's photoprotective and antioxidant properties give it commercial value in cosmetics and medicine [75]. Moisturizing chemicals have side effects like contact sensitivity and estrogenicity on human skin, with harm to aquatic environments also, cyanobacteria offer superior substitutes to commercially manufactured antioxidants used in pharmaceutical and food industries, providing carotenoids, phycobiliproteins, phenolics, glutathione, scytonemin, MAAs, and vitamins like ascorbate and tocopherol [76].

Scytonemin stands out amongst natural products due to its cellular location, strong UV-A and violet-blue absorption, and high Sun Protection Factor (SPF) value. Extracellular substances with high-water retention capacity, can serve as moisturizers in cosmetic products. The demand for natural ingredients in cosmetics is rising, as synthetic inorganic UV filters like titanium dioxide ($TiO_2$) and zinc oxide (ZnO) in sunscreen products produce highly oxidizing radicals [77]. Scytonemin, as a natural sunscreen compound, garners interest from dermatologists and cosmetic industries for skin protection [78, 79]. Producing scytonemin sunscreen synthesized by *Lyngbya notarisii* would be cost-effective [80]. Scytonemin from Antarctic cyanobacterium *Nostoc commune* exhibits a high SPF value and scavenges free radicals, suggesting its potential as a natural UV sunscreen cream ingredient [81].

Beyond its UV-A shielding, scytonemin finds biomedical applications due to its anti-proliferative and anti-inflammatory activities without chemical toxicity [82-83]. Studies with *Nostoc commune* demonstrate scytonemin's antioxidant and radical scavenging activity, potentially preventing UV-induced cellular damage [23, 84, 85]. While scytonemin's antioxidant activity varies across strains like *Lyngbya sp. CU2555*, it still shows radical scavenging ability [34]. Scytonemin synthesized by *Leptolyngbya mycodia* acts as a potent antioxidant, reducing DPPH radicals [20]. Its role in scavenging reactive oxygen species and controlling cancer cell growth is noteworthy [86]. Scytonemin inhibits skin inflammation by down-regulating NF-κB activity [87], regulates human fibroblasts and endothelial cells proliferation [83, 84], and inhibits human polo-like kinase 1 (target for anticancer drugs) [88, 89]. It can suppress human T-lymphoid Jurkat cell growth [90], and LPS/IFNc-stimulated NO production in murine macrophage RAW264 cells [91]. Scytonemin can also restraint the activity of other kinases like Myt1, cyclin B, checkpoint kinase1, and protein kinase C [92], making it a promising small-molecule drug. *Leptolyngbya* holds significant commercial potential in scytonemin synthesis and ecological biotechnology [93]. Various medicinal and agriculturally important bioactive secondary compounds from cyanobacteria have been identified [94], indicating their potential to produce natural substances sustainably.

## Conclusions

Scytonemin, a secondary metabolite produced by cyanobacteria, holds significant market potential due to its varied roles as a UV protectant and antioxidant relevant to anhydrobiosis. Its stability against various stresses and its photo-protective abilities suggest its potential application as a sunscreen. *Scytonema* sp. stands as a promising candidate for bioremediation of saline soils while producing valuable metabolites like scytonemin [95]. However, comprehensive studies on the physiological, biochemical, and molecular aspects, as well as the presence of effective UV-screening/absorbing compounds in these organisms, are still lacking. Therefore, further research is crucial to explore the ecological, industrial, and pharmaceutical applications of scytonemin. Metabolic engineering techniques are expected to play a pivotal role in attaining cost-effective biosynthesis of scytonemin in the future.

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### Conflict of interest

The authors confirm that this article's content has no conflict of interest.

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