World Journal of
Pharmacy and Medical Science

ISSN: 3049-3501
Impact Factor: 5.157
CODEN (USA): WJPMAA

Review Article
2026 Volume 2, Issue 11
Page No.: 84-89

SHIKIMIC ACID BIOSYNTHESIS AND ITS ROLE IN THE PRODUCTION OF AROMATIC AMINO ACIDS AND BIOACTIVE SECONDARY METABOLITES

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Article Received: 06 October 2026 Article Review: 27 October 2026 Article Accepted: 17 November 2026

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DOI: https://doi.org/10.5281/zenodo.24500033

How to cite this Article: Dr. Tanima Debnath Sarkar (2026). SHIKIMIC ACID BIOSYNTHESIS AND ITS ROLE IN THE PRODUCTION OF AROMATIC AMINO ACIDS AND BIOACTIVE SECONDARY METABOLITES. World Journal of Pharmacy and Medical Science, 2(11): 84-89.

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ABSTRACT

Shikimic acid is a key metabolic intermediate in the shikimate pathway, a biosynthetic route found in plants, algae, fungi, and bacteria but absent in animals. The pathway begins with the condensation of phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P) to form 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP), which is subsequently converted into 3-dehydroquinic acid, 3-dehydroshikimic acid, and finally shikimic acid through a series of enzyme-catalysed reactions. Following its biosynthesis, shikimic acid is phosphorylated to shikimate-3-phosphate and converted into 5-enolpyruvylshikimate-3-phosphate (EPSP), which is subsequently transformed into chorismic acid, the final product of the shikimate pathway. Chorismic acid serves as the universal precursor for the biosynthesis of the aromatic amino acids, phenylalanine, tyrosine, and tryptophan. These amino acids further participate in the formation of numerous secondary metabolites, including flavonoids, lignin, tannins, alkaloids, and phenolic compounds. In brown algae such as *Padina gymnospora*, these metabolites play important roles in antioxidant defense, UV protection, herbivore deterrence, antimicrobial activity, and adaptation to environmental stress. Therefore, shikimic acid acts as a crucial metabolic link between primary metabolism and the biosynthesis of diverse bioactive compounds essential for growth, survival, and ecological adaptation.

KEYWORDS: Shikimic acid, Shikimate pathway, Biosynthesis, Phenolic compounds, Padina gymnospora, Aromatic amino acids, Chorismic acid, Antioxidant activity.

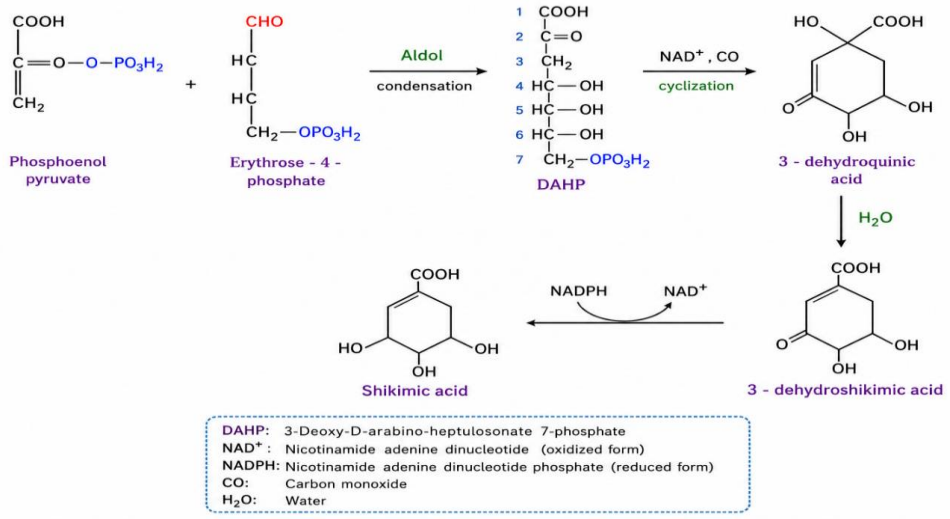


Fig. 1: Graphical abstract.

INTRODUCTION

Brown seaweeds are rich sources of bioactive compounds, including polyphenols, phlorotannins, flavonoids, alkaloids, sterols, sulfated polysaccharides, proteins containing essential amino acids, vitamins, minerals, and polyunsaturated fatty acids (PUFAs), making them valuable for nutritional and therapeutic applications.[1,2] These marine-derived bioactive compounds have attracted considerable attention because of their potential use in functional foods, nutraceuticals, pharmaceuticals, cosmetics, and biomedical products due to their antioxidant, anti-inflammatory, antimicrobial, anticancer, and immunomodulatory properties.[3,4] Fucoxanthin, the characteristic carotenoid pigment responsible for the brown coloration of Phaeophyceae, exhibits potent antioxidant, anti-obesity, antidiabetic, anti-inflammatory, and anticancer activities.[1,5] Fucoidan, a sulfated polysaccharide rich in L-fucose, possesses anticoagulant, antiviral, antioxidant, anti-inflammatory, anticancer, and immunomodulatory activities, with its biological efficacy depending on molecular weight, sulfation pattern, and structural composition.[2,6] Alginates (alginic acid) are linear polysaccharides composed of β-D-mannuronic acid and α-L-guluronic acid residues. Their biocompatibility, biodegradability, non-toxicity, and gel-forming properties have led to widespread applications in food technology, drug delivery, tissue engineering, and wound healing.[7] Laminaran, a storage β-(1→3)-glucan with β-(1→6) branching, exhibits antioxidant, immunostimulatory, antimicrobial, and anticancer properties, making it a promising bioactive polysaccharide for pharmaceutical applications.[8] Brown seaweeds contain high concentrations of nutritionally important PUFAs, including linoleic acid (LA), arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), as well as phytosterols such as fucosterol and isofucosterol, which contribute to cardiovascular, anti-inflammatory, and metabolic health.[4,9] Phlorotannins are unique polyphenolic compounds exclusive to brown algae that function in UV protection, antioxidant defense, herbivore deterrence, and stress adaptation while exhibiting antioxidant, antidiabetic, anti-inflammatory, antimicrobial, anticancer, neuroprotective, and antiallergic activities.[10,11] Brown seaweed species such as Ecklonia cava and Eisenia arborea are particularly rich in phlorotannins. Compounds such as phlorofucofuroeckol A have demonstrated significant antiallergic, antioxidant, anti-inflammatory, and antidiabetic activities, highlighting their potential in pharmaceutical development.[11,12] Overall, the diverse chemical composition and broad spectrum of biological activities exhibited by brown seaweeds make them valuable resources for developing novel functional foods, nutraceuticals, pharmaceuticals, and biomedical products.[4,13]

Brown Seaweed *Padina gymnospora*

Padina gymnospora is a nutritionally rich brown seaweed**,** containing high levels of proteins, carbohydrates, lipids, essential amino acids, vitamins, minerals, and diverse secondary metabolites, making it a valuable marine resource for nutritional and pharmaceutical applications.[14,15] Among the essential amino acids, leucine has been reported as the most abundant, with a concentration of 5.79 ± 0.06 mg g^{-1} dry weight (DW), highlighting the nutritional value of *P. gymnospora* as a potential dietary supplement.[14] The presence of phenolic compounds, flavonoids, phlorotannins, sterols, and other bioactive metabolites contributes to the strong antioxidant capacity of *P. gymnospora*, supporting its potential use in the development of natural antioxidant formulations and encouraging its commercial cultivation.[14,15] Morphologically, *P. gymnospora* possesses a fan-shaped (flabellate to lacerate) thallus that may reach up to 20 cm in length and is attached to rocky substrates by a rhizoidal holdfast. The thallus is partially or completely calcified and exhibits characteristic inward-curled margins during early development.[16,17] The reproductive structures of P. gymnospora include concentric bands of phaeophycean hairs and sporangial sori, with ovoid to pyriform sporangia producing four spores upon maturation. Gametophytes are generally dioecious, although monoecious individuals have also been reported.[16,18] Although comparatively less explored than other brown algae, *P. gymnospora* exhibits considerable pharmacological potential due to its diverse secondary metabolites, including bromophenols, diterpenes, sterols, and phlorotannin.[19,20] Extracts and purified compounds from *P. gymnospora* have demonstrated antioxidant, antimicrobial, antiviral, anti-inflammatory, cytotoxic, immunostimulatory, hepatoprotective, cardioprotective, anti-obesity, hypolipidemic, and anticancer activities, highlighting their potential for pharmaceutical, nutraceutical, and biomedical applications.[15,19,20] Despite the structural complexity of several bioactive metabolites, such as bromophenols and xenicane diterpenes, which complicates their structural characterization and chemical synthesis, these compounds remain attractive candidates for future drug discovery and marine biotechnology research.[19] See Fig2.



(a)



(b)

Division	Phaeophyta
Class	Phaeophyceae
Order	Dictyotales
Family	Dictyotaceae
Genus	Padina
Species	Gymnospora

(c)

Fig. 2: *Padina gymnospora* (a) Habit; (b) Thallus; (c) Systematic Position.

Background

India, located between 8.04°–37.06° N latitude and 68.07°–97.25° E longitude, possesses an extensive coastline of approximately 7,500 km, providing favorable environmental conditions for the growth and diversity of marine macroalgae.[21] Padina gymnospora is widely distributed along the southeast coast of India, particularly in Tamil Nadu and the Union Territory of Puducherry, with major occurrences reported from Krusadai Island (9.14° N, 79.13° E), Idinthakarai (8.10° N, 77.43° E), Rameswaram, Tuticorin, and the Gulf of Mannar Biosphere Reserve.[16,22]

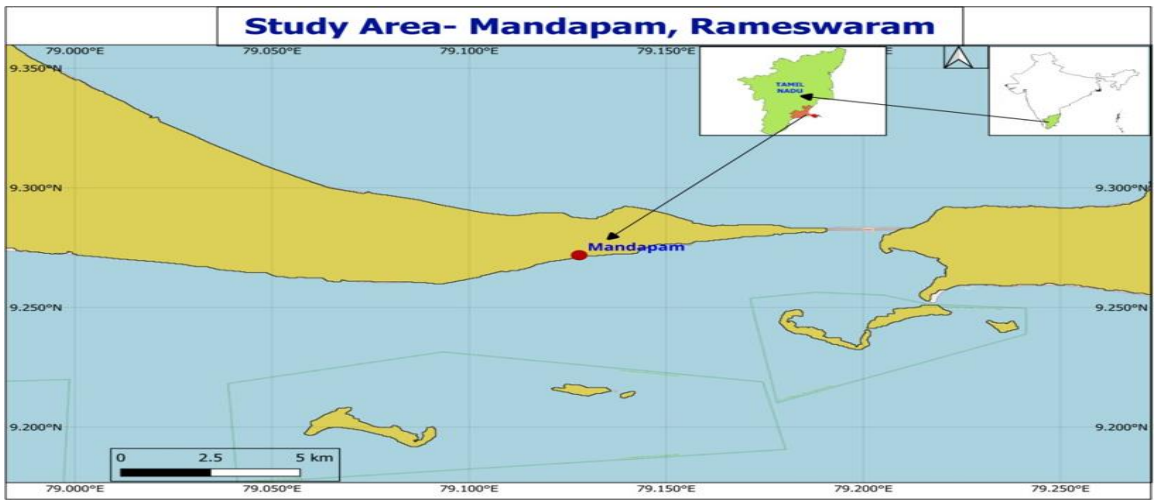


Fig. 3: Map: -*Padina gymnospora* founds Gulf of Mannar, Tuticorin located (8.76°42″ N; 78.13° 48″ E) at Rameswaram in Tamil Nadu in India.

Padina gymnospora contains diverse phytochemicals, including fatty acids, phenolics, sterols, and other bioactive metabolites with significant pharmaceutical potential.[23] Major phytochemicals identified include palmitic acid, stearic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid, stearidonic acid, eicosapentaenoic acid (EPA), palmitoleic acid, and nonadecanoic acid.[23,24] These phytochemicals exhibit antioxidant, anti-inflammatory, antimicrobial, cardioprotective, and nutraceutical properties, highlighting the medicinal importance of *P. gymnospora*.[14,23]

Shikimic pathway[25,26]

The shikimic acid pathway in *Padina gymnospora* is an essential metabolic pathway responsible for the biosynthesis of aromatic amino acids, including phenylalanine, tyrosine, and tryptophan, which serve as precursors for various bioactive phytochemicals. These secondary metabolites exhibit antioxidant, anti-inflammatory, and antimicrobial properties and play important roles in the alga's defense, stress tolerance, and potential therapeutic applications.

Glycolysis (Pentose Phosphate Pathway)

↓ ↓ ↓

Phosphoenolpyruvate (PEP) + Erythrose-4-phosphate (E4P)

↓

(Condensation via DAHP synthase)

3-Deoxy-D-arabino-heptulosonate 7-phosphate (DAHP)

↓

(Reduction and cyclization via DHQS synthase)

3-Dehydroquinate (DHQ)

↓
(Dehydration via DHQD synthase)
3-Dehydroshikimate (DHS)
↓
(Reduction via shikimate dehydrogenase)
Shikimate (Shikimic acid)
↓
(Phosphorylation via shikimate kinase)
Shikimate-3-phosphate (S3P)
↓
+ Phosphoenolpyruvate (PEP)
↓
(Condensation via EPSP synthase)
5-Enolpyruvylshikimate-3-phosphate (EPSP)
↓
(Reaction via chorismate synthase)
Chorismate (Precursor to aromatic amino acids)
↓ ↓ ↓
Phenylalanine, Tyrosine, Tryptophan

Shikimic acid: Shikimic acid [CAS Number 138-59-0], commonly present in its ionized form as shikimate, is a naturally occurring cyclitol containing a cyclohexene ring and a cyclohexanecarboxylic acid structure. It is an essential intermediate in the shikimate pathway, which is responsible for the biosynthesis of aromatic amino acids and numerous secondary metabolites in plants, algae, fungi, and microorganisms. The compound was first isolated in 1885 from the Japanese star anise (Illicium anisatum), locally known as Shikimi, by the Dutch chemist Johan Fredrik Eykman. Its complete chemical structure was determined nearly five decades later, establishing its importance as a key metabolite in plant and microbial biochemistry. The shikimate pathway is a biosynthetic pathway that leads to two major groups of products:

- Aromatic amino acids (primary metabolism)
- Secondary metabolites (including alkaloids, phenolics, flavonoids, lignin, tannins, etc.)

Shikimic Acid Pathway: Biosynthesis of Aromatic Amino Acids and Secondary Metabolites

The shikimic acid pathway is a seven-step biosynthetic pathway present in plants, algae, fungi, and bacteria but absent in animals. In Padina gymnospora, this pathway converts simple carbon compounds derived from photosynthesis into chorismic acid ($C_{10}H_{10}O_6$), the universal precursor of aromatic amino acids and numerous secondary metabolites. The pathway begins with phosphoenolpyruvate (PEP; $C_3H_5O_6P$) from glycolysis and erythrose-4-phosphate (E4P; $C_4H_9O_7P$) from the pentose phosphate pathway. These substrates are condensed by DAHP synthase to produce 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP), which is subsequently converted to shikimic acid ($C_7H_{10}O_5$) through a series of enzymatic reactions. Finally, shikimic acid is transformed into chorismic acid, which acts as the major branching point for metabolite biosynthesis.[25,26]

- **Biosynthesis of Aromatic Amino Acids (Primary Metabolism)**

The first major branch from chorismic acid leads to the biosynthesis of the aromatic amino acids phenylalanine ($C_9H_{11}NO_2$), tyrosine ($C_9H_{11}NO_3$), and tryptophan ($C_{11}H_{12}N_2O_2$). These amino acids are synthesized by incorporating nitrogen derived from ammonia (NH_3/NH_4^+) through glutamine- and glutamate-dependent reactions. Carbon skeletons originate from carbon dioxide (CO_2) that has been fixed during photosynthesis into carbohydrates, which are then metabolized to PEP and E4P. These aromatic amino acids are essential for protein synthesis and serve as precursors for numerous specialized metabolites.[25]

- **Biosynthesis of Secondary Metabolites**

The second major branch utilizes the aromatic amino acids to synthesize a wide variety of secondary metabolites. Phenylalanine enters the phenylpropanoid pathway to produce phenolic acids, flavonoids, lignin, coumarins, and tannins. Tyrosine serves as a precursor for isoquinoline alkaloids, tocopherols, and quinones, whereas tryptophan gives rise to indole alkaloids and plant growth regulators. In brown algae such as Padina gymnospora, the shikimate pathway also provides precursors for phlorotannins and other phenolic compounds, which contribute to antioxidant activity, UV protection, antimicrobial defense, herbivore resistance, and environmental stress tolerance.[26,27]

- **Carbon and Nitrogen Flow**

The carbon atoms incorporated into shikimate-derived metabolites originate from atmospheric carbon dioxide (CO_2) fixed during photosynthesis. The nitrogen required for amino acid biosynthesis is supplied by ammonia (NH_3/NH_4^+) assimilated into glutamine and glutamate before being transferred to aromatic amino acids. Thus, CO_2 provides the carbon skeleton, while NH_3 provides the amino group, together enabling the synthesis of amino acids and subsequent secondary metabolites.

Compound	Molecular Formula	Function
Carbon dioxide	CO_2	Carbon source
Ammonia	NH_3	Nitrogen source
Phosphoenolpyruvate (PEP)	$C_3H_5O_6P$	Initial substrate
Erythrose-4-phosphate (E4P)	$C_4H_9O_7P$	Initial substrate
Shikimic acid	$C_7H_{10}O_5$	Central intermediate
Chorismic acid	$C_{10}H_{10}O_6$	Branch-point metabolite
Phenylalanine	$C_9H_{11}NO_2$	Aromatic amino acid
Tyrosine	$C_9H_{11}NO_3$	Aromatic amino acid
Tryptophan	$C_{11}H_{12}N_2O_2$	Aromatic amino acid

- **Atom Economy and Shikimic Acid Biosynthesis**

Atom economy is one of the 12 principles of green chemistry, introduced by Barry Trost (1991).[28] It measures how efficiently the atoms of the reactants are incorporated into the desired product. A reaction with high atom economy produces little or no waste, making it environmentally friendly.

The atom economy is calculated as

$$\text{Atom Economy} = \frac{\text{molecular wt. of desired product}}{\text{molecular wt. of all products}} \times 100\ \%$$

Relation to the Shikimate Pathway

In the shikimate pathway, shikimic acid is synthesized from phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P) through enzyme-catalysed reactions.

Overall simplified reaction

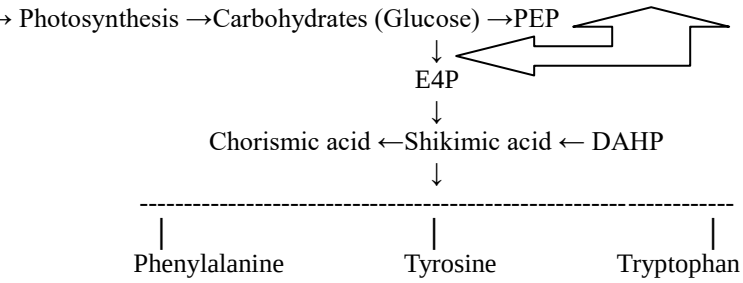
PEP+E4P⟶DAHP⟶Shikimic acid

During this pathway

- Carbon atoms originate from CO_2 fixed during photosynthesis.
- Most of these carbon atoms are retained throughout the pathway to form shikimic acid and, subsequently, aromatic amino acids.
- Enzymes catalyze the reactions with high specificity, minimizing unwanted side products.
- The pathway operates under mild conditions (aqueous medium, ambient temperature, neutral pH), reducing energy consumption and hazardous waste.

Thus, the biosynthesis of shikimic acid is considered an example of a high atom economy biological process, since most atoms from the substrates are incorporated into the final metabolites.

Carbon Flow:[25,26]



Significance

- High atom utilization due to enzymatic catalysis.
- Minimal by-product formation, reducing waste.
- Energy-efficient because reactions occur under physiological conditions.
- Environmentally sustainable, aligning with green chemistry principles.

CONCLUSION

Shikimic acid is a vital metabolic intermediate linking primary and secondary metabolism. Its biosynthetic pathway exhibits high atom economy, efficiently producing aromatic amino acids and bioactive compounds essential for growth, defense, and adaptation.

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