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P Mohitha
Department of Nano Science & Technology, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

S Haripriya
Department of Nano Science & Technology, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

A Lakshmanan
Department of Nano Science & Technology, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

Corresponding Author:
S Haripriya
Department of Nano Science & Technology, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

Elucidation of biosynthetic pathway of the plant bioactives from leaves of soursop (*Annona muricata* Linn.)

P Mohitha, S Haripriya and A Lakshmanan

Abstract
Soursop, previously known as “cancer killer tree” is widely used as a complimentary medicine to treat various types of cancer patients. At present, no direct evidence is available as to the biosynthetic pathway of its unusual skeleton. To provide guidance as to possible biosynthetic precursors, construction of biosynthetic pathway based on the secondary metabolites obtained from soursop leaf phytochemicals. This paper shows biosynthetic scheme based in sound biosynthetic principles of compounds newly found in nature or those difficult to tackle by conventional means.

Keywords: Soursop, secondary metabolites, biosynthetic pathway, KEGG database

1. Introduction

Nature is a unique source of phytochemical diversity many of them possesses interesting biological activities and medicinal properties. Plant based secondary metabolites have played a significant role in developing multi-targeted drugs towards treatment of various human ailments. During long period evaluation, plants struggling to survive gradually gain the ability to synthesize various kinds of secondary metabolites with significant bioactivities (Alali, *et al*., 1999) [1]. Based on the structures, the secondary metabolites can be classified into alkaloids, flavonoids, phenylpropanoids, quinines, steroids, tannins and proteins (Oberlies *et al*., 1995) [2] as the compounds are biosynthesized through series enzyme catalyzed reactions. Gene cloning, transformation and regulation have achieved significant progress in biosynthetic pathway of secondary metabolites (Romek *et al*., 2015) [3]. For instance, previously reported biosynthetic pathway elucidation and gene regulation of anti-cancer compounds from *Catharanthus roseus* (Guirimand *et al*., 2011) [4]. In such a way soursop (*Annona muricata* Linn.) of Annonaceae family commonly known as Graviola or Guanabana is being grown in warm tropical regions of the world, wherein every part of the tree possesses numerous medicinal properties. Phytochemical investigations from *A. muricata* leaves revealed the presence of phenols, saponins, terpenoids, flavonoids, isoquinoline alkaloids and annonaceous acetogenins (Mishra *et al*., 2013) [5]. The extracts as well as different isolated bioactive constituents of *A. muricata* have been reported to possess anti-cancer, antibacterial and antifungal actions, as well as, its antinociceptive and anti-inflammatory activities (Sousa *et al*., 2010) [6].

As a medicinally important natural product, Soursop shows some interesting features, but to elucidate a biosynthetic pathway by which it is produced is problematical. In addition, the structural features could arise from a number of putative pathways. To obtain guidance as to the possible primary precursors and intermediates involved, the novel approach of this study was to determine the entire biosynthetic pathway from compounds obtained from leaves of *A. muricata* to identify key metabolic intermediates. Then the metabolic as well as biosynthetic pathways for the identified phytochemicals from leaves were constructed. Till date, there is no report on construction of metabolic pathways from previously reported bioactive compounds of leaves of *A. muricata.*

2. Materials and Methods

Secondary metabolites present in leaves of *A. muricata* were obtained from previously reported studies. The structure of the compounds was retrieved from PubChem database. 52 common metabolites were obtained from previous reports. All molecules in the dataset are enriched with characteristics being effective candidates to optimize the search for new therapeutic agents.

Construction of metabolic pathway was done by using KEGG pathway database (GenomeNet).

3. Results and Discussion

Elucidation of the biosynthetic pathway of natural products is often prerequisite to the characterization of the enzymes involved and the identification of the intermediates encoding them. Based on the results of previous studies, biosynthetic pathway is constructed using an array of enzymes presents a hierarchial organization of the compounds with precursor. A total 52 compounds were identified from previous reports by Gavamukulya *et al*., (2015) [7]. The metabolic pathways are constructed using KEGG pathway database as shown in (Fig.1). Most phenolic compounds are derived from the phenylpropanoid pathway, and the bioactive compound 2-hydroxy 5- methyl chalcone come under this pathway. Chalcones represents an important group of polyphenolic family, possesses interesting spectrum of biological activities, including antioxidative, anti-inflammatory and anti-cancer potential. Terpenoids are the most diverse class of chemical compounds comprising of monoterpenes, sesquiterpenes, diterpenes and triterpenes with wide range of bioactivity. Most of the terpenoids are synthesized from mevalonate biosynthetic pathway and the bioactive compounds such as humulene, murolene, squalene and germacrene are sesquiterpenoid compounds comes under this pathway. Sesquiterpenoids represents most important bioactivity group shows anti-cancer, antibacterial and anti-fungal activity. Fatty acid derivatives are major constituents of biological membranes and they play crucial roles in normal cell physiology. Palmitic acid is used as precursor for the synthesis of complex lipid molecules using fatty acid biosynthetic pathway. From previous reports of GC-MS analysis, resulted in the identification of major fatty acids such as hexadecanoic acid, linoleic acid, arachidic acid, oleic acid and nonadecane are the detected metabolites falls under this pathway having anti-cancer, anti-inflammatory and anti-diabetic effects. The construction of metabolic pathways for the detected compounds would be useful in synthesis of potential candidates with potent bioactivity by manipulating precursor through biosynthetic pathway.

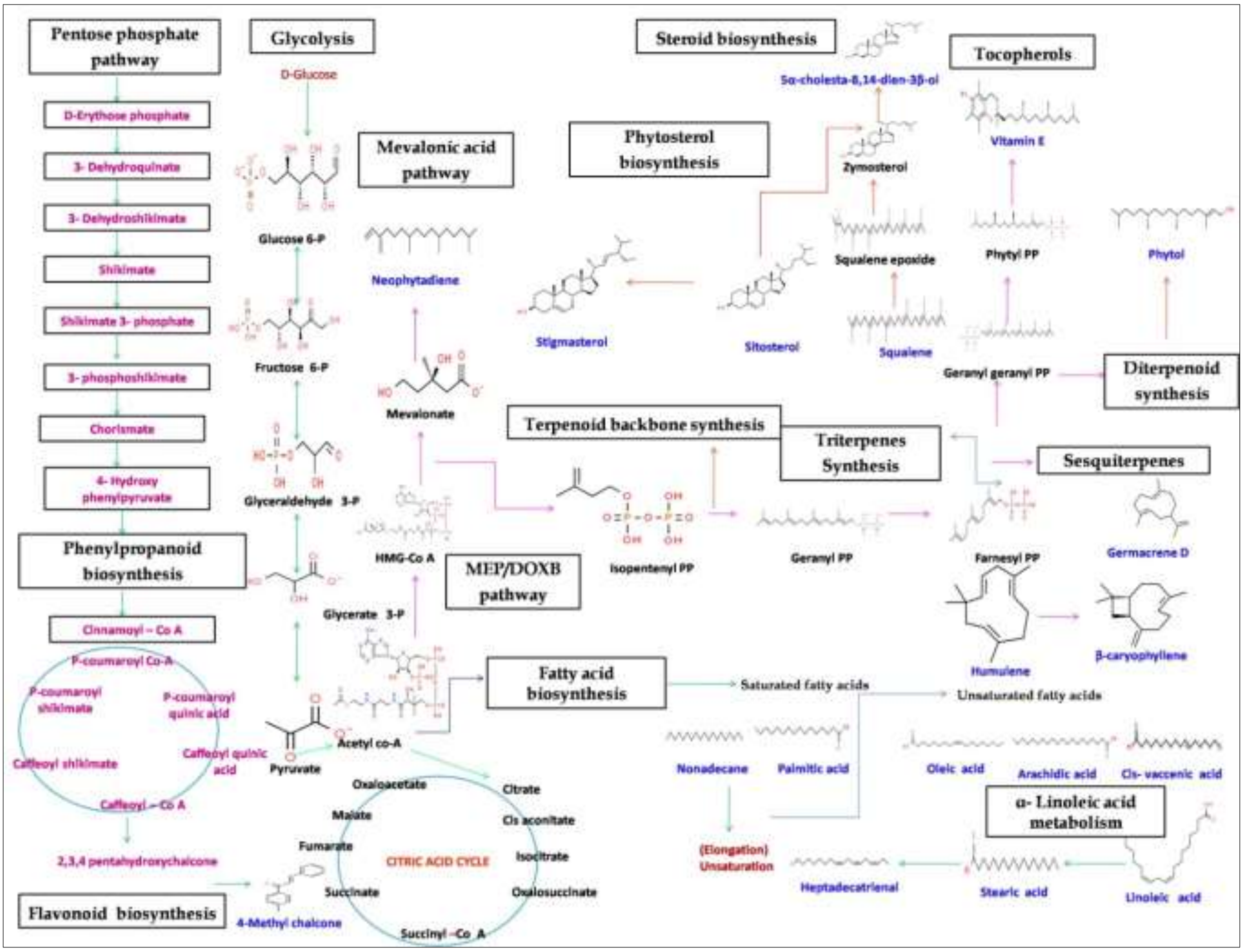

Fig 1: Metabolic pathway map with associated phytochemicals extracted from leaves of *A. muricata*

In conclusion, major phytochemicals obtained from soursop leaves as reported earlier exhibited a wide range of bioactivity. This was the first report on construction of biosynthetic pathway from soursop leaf phytochemicals. As a conventional approach to study its probable biosynthetic precursors, enzymatic steps and intermediate metabolites is not feasible. The concept of biosynthetic pathway by examining the secondary metabolites within the soursop leaves and constructing the biosynthetic pathway in terms of known plant biochemical processes that might be involved in a soursop phytochemicals.

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