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Elucidation of biosynthetic pathway for plant bioactives from aerial portion of Green Chireta (*Andrographis paniculata* Nees.)

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ABSTRACT

Green chireta, previously known as "king of bitters" 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 green chireta 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.

Key words: *Green chireta, Secondary metabolites, Biosynthetic pathway, KEGG database*

Introduction

Many plants present in the environment are eminent producers of primary and secondary metabolites exhibiting various biological activities as well as medicinal properties. Secondary metabolites produced by plants are generally small organic molecules which is not essential for growth, development and reproduction of plants whereas these secondary metabolites are very useful in many modern medicines and medicinal herbs due to their potent action against various human diseases. Over 50,000 secondary metabolites have been discovered in the plant kingdom. These secondary metabolites can act as medicine either as a single compound or even as mixture helping in synergizing or aggravating the effects of other compounds present. They can be classified based on the pathway by which they are synthesized. The secondary metabolites can be classified as alkaloids, phenols, flavonoids, saponins, terpenoids, tannins, glycosides, phytosterol, and proteins (Widjajakusuma *et al.*, 2018). A simple classification includes three main groups: terpenoids (polymeric isoprene derivatives and biosynthesized from acetate via the mevalonic acid pathway), phenolics (biosynthesized from shikimate pathways, containing one or more hydroxylated aromatic rings) and the extremely diverse alkaloids (non-protein nitrogen-containing compounds, biosynthesized from amino acids such as tyrosine) (Seca and Pinot, 2018). These components produced via the biosynthetic pathways utilize numerous catalytic enzymes and chemical intermediates. The breakthrough in the biosynthetic pathway of secondary metabolites has been accomplished due to gene cloning, transformation and its regulation. The

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gene regulation research on the anticancer compounds namely vincristine and vinblastin from *Catharanthus roseus* is a recent study on the biosynthetic pathway of secondary metabolites (Mei *et al*., 2010). Green chireta (*Andrographis paniculata* Nees.) being a perennial herb is widely grown in tropical and sub-tropical regions of the world, is consisting of enormous medicinal values. Pandey *et al*. (2019) and Widjajakusuma *et al.* (2018) reported the presence of various phytochemicals namely alkaloids, flavonoids, saponins, terpenoids, tannins, glycosides, phytosterol, proteins and andrographolide from the aerial plant extract of *A. paniculata*. The whole plant extract of *A. paniculata* and its isolated phytoconstituents have reports on anticancer, anti-inflammatory, antiallergic, immunostimulatory, antithrombotic, antibacterial, antiviral, hypoglycemic and hypotensive activities (Parveen *et al*., 2019).

Though green chireta is a medicinally important herbal plant, elucidating its biosynthetic pathway is enigmatic. Moreover, there a number of putative pathway from which their structure could be elucidated. The main aim of this study is to deduce the complete biosynthetic pathway of *A. paniculata's* bioactives from its aerial portion through the possible primary precursors and intermediates involved. Thus through the distinguished phytochemicals from the aerial portion of the plant, the metabolic as well as biosynthetic pathways were constructed. To the best of our knowledge, this is the first report on construction of metabolic pathways from previously reported bioactive compounds from the aerial portion of *A. paniculata.*

Materials and Methods

Secondary metabolites were obtained from previously reported studies on the aerial portion of *A. paniculata*. The PubChem database was used to retrieve the compounds structure. Previous reports conclude 44 common metabolites which were chosen for the study. The repository containing all the molecules is enriched with therapeutic values against various ailments. Using KEGG pathway database (GenomeNet) the biosynthetic pathway was constructed.

Results and Discussion

Biosynthetic pathway elucidation of many natural compounds is important as it postulates importance of the enzymes involved and also helps in the identification of the intermediates encoding them. Using the precursors under a hierarchical organization the biosynthetic pathway is constructed based on the previous reports and studies. A total of 44 compounds were identified from previous report by Nayak *et al*. (2020). The biosynthetic pathways are constructed using KEGG pathway database as shown in (Fig.1). 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 fenchane, lanostane, roburic acid, 9, 19-Cyclolanostane and gibbane 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 palmitic acid, decanoic acid, behenic acid, lauric acid, stearic acid, a-linoleic acid and linolenelaidic acid are the detected metabolites falls under this pathway having anti-cancer, anti-inflammatory and antidiabetic effects. Carotenoids are class of phytoconstituents which are lipophilic in nature synthesized through ioprenoid pathway exhibiting antioxidant and anti-inflammatory properties. The most prevalent bioactive compound under this pathway is phytoene, lycopene, rhodopin and tetrahydrospirilloxanthin. Steroids are biosynthetically derived phytoconstituents from triterpene backbones. Most of the steroids in this steroid pathway includes cholestane, cholecalciferol, 5a-pregnane3,20 dione, 3-hydroxyspirost-8-en-11-one. These plant steroids possess activities like anti-tumor, immunosuppressive, hepatoprotective, antibacterial, cytotoxic and cardiotonic activity. 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.

Conclusion

The aerial portion of green chireta has been reported

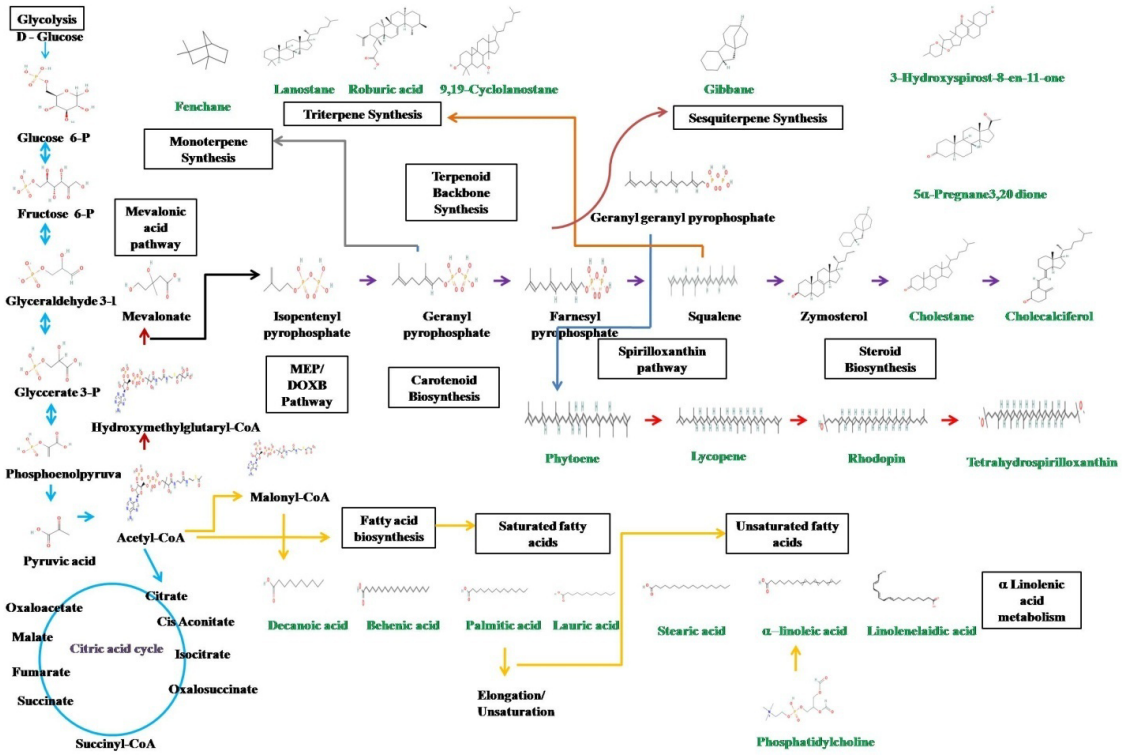

Fig. 1. Metabolic pathway map with associated phytochemicals extracted from aerial portion of *A. paniculata*

with numerous phytochemicals revealing their therapeutic importance and several bioactivities. This was the first report on construction of biosynthetic pathway from aerial portion of *A. paniculata* phytochemicals. It is highly impractical to identify and study its probable biosynthetic precursors, steps involved in the enzymatic reaction and finding out its intermediate metabolites through conventional approach. Hence the concept of biosynthetic pathway construction through the known green chireta secondary metabolites leading to a plant biochemical processes that might be involved in a green chireta phytochemicals. The present study enhances the traditional use of green chireta which possess several known phytochemicals. Hence on isolating these pharmacologically important phytoconstituents, new drugs can be designed for treating for various diseases.

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