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Decoding the Triterpenoid Gymnemic Acid Biosynthetic Pathway in Gymnema Sylvestre

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ABSTRACT

Gymnemic acid, a bioactive compound with potential medicinal properties, is synthesized by a complex enzymatic process known as the denovo biosynthetic pathway. This pathway involves a series of well-coordinated steps starting from acetyl Co A till the synthesis of gymnemic acid, each series of reaction is catalyzed by biochemical conversion involving 15 enzymes. The enzymes required to catalyze the conversion of cochalicic acid to acacic acid and acacic acid to gymnemic acid have not been reported previously. Hence, this study highlights the link missing in the complex biomolecular transformation leading to synthesis of gymnemic acid. This is the first report to identify these enzymes as acacic acid synthase and gymnemic acid synthase. Additionally, organized schematic representation of biosynthetic pathway was deduced.

Keywords: *Gymnema sylvestre, Gymnemic acid, Triterpenoid, Gurmarin, Biosynthetic pathway*

1. INTRODUCTION

Gymnema sylvestre, commonly known as gurmar or "sugar destroyer," "periploca of the woods" and "Australian cowplant" it is a captivating medicinal herb, native to tropical regions of India, Africa, and Australia. This plant has been used for centuries in traditional ayurvedic medicine. Owing to its potential ability to treat various illness, *Gymnema sylvestre* gained popularity for use as a natural and alternative therapies (1). In earlier days, people used to chew the leaves of *Gymnema sylvestre* or brew into tea to control their blood sugar levels. The leaves are known for their ability to suppress sweetness, and can be deduced as an intense contributor in enhancing its therapeutic properties. This makes it an interesting herb for the treatment of diabetes and sugar cravings. Apart from its anti-diabetic properties, this herb is used to treat/improve various health conditions such as, improve digestion, relieve inflammation, suppress appetite and promote weight management (2). Some studies suggest that this herb may affect the brain's hunger and satiety mechanisms, leading to decreased food intake. However, these findings are still in their infancy and further research is needed to definitively link *Gymnema sylvestre* to weight management. Researchers have also discovered its anti-inflammatory, antioxidant, and antibacterial properties, which may contribute to broader therapeutic potential (3).

1.1 Role of Triterpenoid Gymnemic Acids in Diabetes and Obesity Management

Among the few bioactive compounds derived from *Gymnema sylvester* most significant compounds, known to hold immense potential in the management of diabetes and obesity since the earliest times are Gymnemic acid a triterpenoid glycoside (saponins) and ‘gurmarin’ a peptide that prevents the tongue from detecting sweet flavors by binding to the receptors making

it difficult to distinguish between sweet and sour flavors. *Gymnema sylvestre* hypoglycemic and hypolipidemic effects, highlighting gurmarin-like peptides' potential in sweet taste suppression and their promise as drug scaffolds for developing antidiabetic molecules, supporting its traditional use in medicinal therapies (4, 5).

Gymnemic acids also work with the intestinal lining to prevent the absorption of sugars during digestion. Studies have indicated that extracts of *G. sylvestre* and natural gymnemic acid exhibit inhibitory effects on the release of Gastric Inhibitory Peptide (GIP) in rats (6, 7). The leaf extracts of *G. sylvestre* and purified gymnemic acid interact with glucose receptors, inhibiting glucose-stimulated GIP release in rats. Their unique mechanisms of action, including interference with sugar absorption, insulin stimulation, and lipid metabolism modulation, make them valuable candidates for inclusion in strategies aimed at controlling blood glucose levels (8, 9).

The extract of the plant is known for its antihyperglycemic effect in humans. The reduction in blood sugar levels through the action of Gymnemic acid is attributed to its stimulation of the release of stored endogenous insulin and its interference with glucose receptors. In diabetic patients, the ingestion of *G. sylvestre* extract has been noted to significantly reduce urinary glucose levels (10, 11). Moreover, the activity of insulin-dependent enzymes such as hexokinase, glycogen synthase, glyceraldehyde 3-phosphate dehydrogenase, and glucose 6-phosphate dehydrogenase was found to decrease in hyperglycemic rabbits. Additionally, the activity of insulin-independent enzymes including glycogen phosphorylase, gluconeogenic enzymes, glucose 6-phosphatase, fructose 1,6-diphosphatase, and sorbitol dehydrogenase of the polyol pathway significantly decreased with the administration of *G. sylvestre* (12).

The hexane extract derived from *G. sylvestre* leaves has demonstrated potential anti-obesity effects. It was investigated that following a 45-day regimen of daily consumption of *G. sylvestre* hexane extract, a notable reduction in elevated body weight and excessive body temperature was observed in rats induced with obesity. This hexane extract exhibited significant improvement in lowering cholesterol, triglyceride, LDL, and HDL levels. Furthermore, the anti-obesity potential of the hexane extract from *G. sylvestre* leaves appeared to be more effective compared to the conventional drug, atorvastatin (13, 14). The research findings unveiled that *G. sylvestre* leaf extract has significant potential in lowering cholesterol levels and serves as a natural remedy for addressing obesity.

1.2 Understanding the Molecular Insights of Gymnemic Acid Biosynthetic Pathway

The mevalonate pathway plays a pivotal role in the biosynthesis of triterpenoids, a diverse group of natural compounds with numerous biological activities. Triterpenoids are synthesized from isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP), both of which are intermediates produced within the mevalonate pathway.

The pathway starts with the conversion of acetyl-CoA to mevalonate. Mevalonate is a crucial precursor for the biosynthesis of various isoprenoid compounds, including triterpenoids. Mevalonate is further converted to isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) through a series of enzymatic reactions. IPP and DMAPP are the basic building blocks for the synthesis of all isoprenoids, including triterpenoids. IPP and DMAPP are condensed to form geranyl diphosphate (GPP), farnesyl diphosphate (FPP), and geranylgeranyl diphosphate (GGPP), which are the precursors for various classes of isoprenoids. Triterpenoids are derived from FPP and GGPP, which serve as starting points for the synthesis of different triterpenoid skeletons. Triterpenoids are structurally diverse compounds, and their specific structures are achieved through cyclization, rearrangement, and modification reactions catalyzed by various enzymes. These reactions generate the wide array of triterpenoid compounds found in nature, such as saponins, steroids, and pentacyclic triterpenes (12).

Each enzyme in this pathway plays a crucial role in catalyzing specific reactions, ultimately leading to the synthesis of gymnemic acid. The coordinated action of these enzymes demonstrates the complexity and precision of nature's biochemical processes. Even though significant biochemical information is available However, there is no information in the roadmap about the enzyme that catalyzes the final steps in the production of acacic acid and its conversion to gymnemic acid nor is there an organizational diagram of the biosynthetic pathway, which It is important to understand the important process biological functions. Therefore, this study aimed to deduce the organized representation of the gymnemic acid biosynthetic pathway as well as the enzymes involved.

2. MATERIALS AND METHODS

2.1 Denovo Bio-synthetic Pathway of Gymnemic Acid

The literature survey on the biosynthetic pathway of gymnemic acid showcases the orchestrated efforts of various enzymes to convert simple precursor molecules into the complex and valuable compound, gymnemic acid. Bio-synthetic pathway can be inferred in 5 important steps. In the 1st step Acetyl CoA is carboxylated to malonyl CoA, a key building block for the synthesis of triterpenoid compounds in the presence of enzyme Acetyl CoA Carboxylase. In the 2nd step Malonyl CoA is condensed with isopentenyl pyrophosphate (IPP) to form 2,3-oxidosqualene, the initial triterpenoid precursor in the presence of enzyme Squalene Synthase. In the 3rd step Cyclization of 2,3-Oxidosqualene takes place, where 2,3-oxidosqualene

undergoes cyclization to form beta-amyrin, an important triterpenoid intermediate in the presence of enzyme oxidosqualene Cyclase. In the 4th step the enzyme Cytochrome P450 oxidase catalizes the reaction which supports the formation of Gymnemagenin by oxidizing Beta-amyrin to form gymnemagenin, a triterpenoid aglycone precursor of Gymnemic Acid. In the final step Gymnemagenin is glycosylated by a glycosyltransferase enzyme, resulting in the formation of Gymnemic Acid, the active compound of interest (15).

2.2 Creating the Schematic Representation of the Pathway

The Pathway was created by using bioinformatic tool Chemdraw the main focus was to provide a clear and organized link in the pathway. In this study, we propose a biosynthetic pathway for the production of Gymnemic Acid starting from acetyl CoA. The pathway culminates as acacic acid is transformed into the bioactive compound gymnemic acid, completing the intricate cascade of enzymatic reactions. The pathway involves a series of chemical conversions mediated by specific enzymes.

The pathway initiation begins with the conversion of three molecules of acetyl coenzyme A (Acetyl CoA) into mevalonic acid. This conversion is facilitated by the enzyme isopentenyl phosphate kinase. Mevalonic acid is subsequently transformed into isopentenyl pyrophosphate through the enzymatic action of isopentenyl diphosphate isomerase. Isopentenyl pyrophosphate is converted into geranyl pyrophosphate with the aid of the enzyme prenyl transferase. The synthesis progresses as geranyl pyrophosphate undergoes a transformation into farnesyl pyrophosphate, catalyzed by another prenyl transferase enzyme. Further in the pathway, farnesyl pyrophosphate is converted into squalene, a key intermediate, by the enzyme squalene synthase. Squalene, in the presence of squalene cyclase enzyme, undergoes cyclization to form a structurally important intermediate. The cyclized squalene is then transformed into 2,3 oxidosqualene through the enzymatic activity of oxidosqualene synthase. Continuing the process, 2,3 oxidosqualene is converted into cycloartenol with the assistance of cycloartenol synthase enzyme. A subsequent transformation occurs, where cycloartenol is modified into 24 methylenecycloartenol by the enzyme S-adenosyl transferase. Cycloartenol derivative isomerizes to cycloeucalenol, guided by the action of 24 methylenecycloartenol isomerase enzyme.

Cycloeucalenol undergoes another rearrangement, forming obtusifoliol, under the influence of cyclopropyl isomerase enzyme. The pathway progresses as obtusifoliol transforms into 16 alpha hydroxy beta amyrin, facilitated by beta amyrin synthase enzyme. Maniladiol, an intermediate, is produced from 16 alpha hydroxy beta amyrin through the action of an oxidase enzyme. Continuing the synthesis, maniladiol is converted into cochalic acid with the involvement of another oxidase enzyme. A significant transformation takes place as cochalic acid is converted into acacic acid, which marks a pivotal stage in the pathway. Finally, the pathway culminates as acacic acid is transformed into the bioactive compound gymnemic acid, completing the intricate cascade of enzymatic reactions Fig 1 (16, 17).

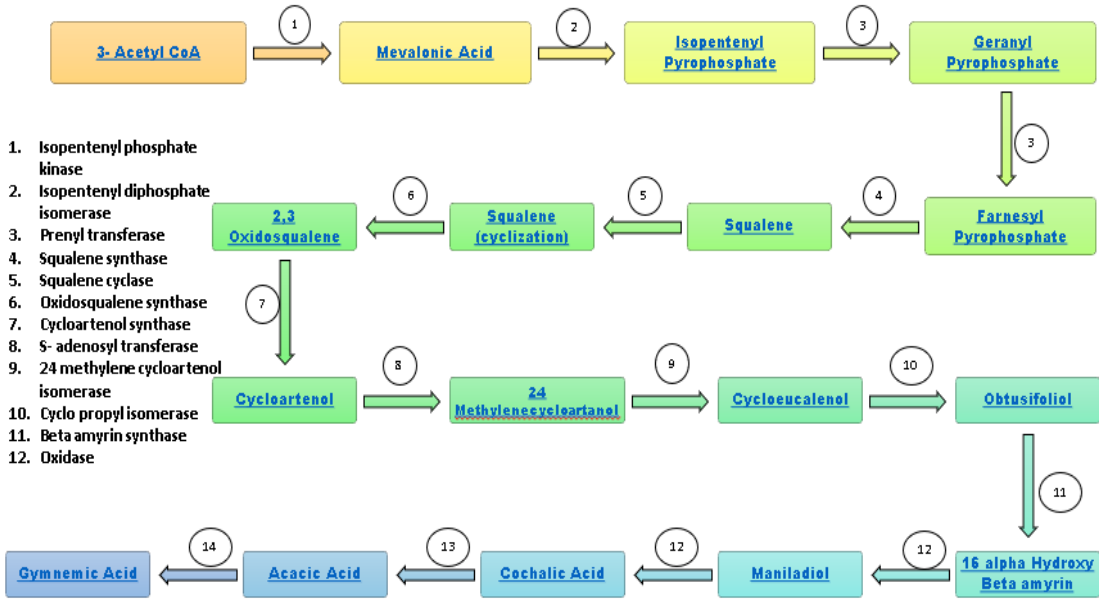

Fig 1: Schematic representation of series of chemical transformation involved in synthesis of Gymnemic Acid along with the enzymes involved in the reaction. 1. Isopentenyl phosphate kinase, 2. Isopentenyl diphosphate isomerase, 3. Prenyl transferase,4. Squalene synthase, 5. Squalene cyclase, 6. Oxidosqualene synthase, 7. Cycloartenol synthase, 8. S- adenosyl transferase, 9. 24 methylene cycloartenol isomerase, 10. Cyclo propyl isomerase, 11. Beta amyrin synthase, 12. Oxidase, 13. Oxidase 14. Acacic Acid Synthase, 15. Gymnemic Acid Synthase.

3. RESULTS AND DISCUSSION

3.1 Enzymes of Gymnemic Acid Pathway

This pathway highlights the intricate molecular transformations of compounds starting from acetyl Co A to synthesis of Gymnemic Acid, for the biochemical transformation fifteen enzymes are involved (Fig 1). in which the enzymes required to catalize the conversion of cochalicacid to acacic acid and from acacic acid to gymnemic acid was not reported earlier this is the 1st report to identify these enzymes. The function of each enzymes are as follows and also the conversions catalyzed by these is shown in the result 3.2:

1. Isopentenyl Phosphate Kinase: This enzyme initiates the pathway by catalyzing the conversion of three acetyl coenzyme A molecules into mevalonic acid, which serves as a precursor for subsequent steps.

2. Isopentenyl Diphosphate Isomerase: Mevalonic acid is then converted into isopentenyl pyrophosphate through the action of this enzyme, enabling the formation of higher isoprenoid intermediates.

3. Prenyl Transferase: This enzyme is responsible for two consecutive steps in the pathway: the conversion of isopentenyl pyrophosphate into geranyl pyrophosphate, and the subsequent transformation of geranyl pyrophosphate into farnesyl pyrophosphate. These reactions build larger isoprenoid structures.

4. Squalene Synthase: Squalene synthase catalyzes the synthesis of squalene from farnesyl pyrophosphate, contributing to the formation of complex steroidal compounds.

5. Squalene Cyclase: Squalene undergoes cyclization in the presence of this enzyme, leading to the formation of a structurally important intermediate in the pathway.

6. Oxidosqualene Synthase: This enzyme is responsible for converting the cyclized squalene into 2,3 oxidosqualene, a critical step leading to diverse triterpenoid compounds.

7. Cycloartenol Synthase: Cycloartenol synthase facilitates the transformation of 2,3 oxidosqualene into cycloartenol, marking a key step toward the production of specialized triterpenes.

8. S-Adenosyl Transferase: In this step, cycloartenol is modified into 24 methylenecycloartenol, introducing additional functional groups into the molecule.

9. 24 Methylenecycloartenol Isomerase: This enzyme isomerizes 24 methylenecycloartenol to cycloeucalenol, contributing to the diversity of triterpene structures.

10. Cyclopropyl Isomerase: Cycloeucalenol undergoes rearrangement to form obtusifoliol, a crucial transformation in the pathway.

11. Beta Amyrin Synthase: Obtusifoliol is converted into 16 alpha hydroxy beta amyrin by this enzyme, leading to the synthesis of specialized triterpenoids.

12. Oxidase: The pathway progresses as 16 alpha hydroxy beta amyrin is oxidized to form maniladiol, introducing additional oxygen atoms into the molecule.

13. Oxidase: Maniladiol is further oxidized to cochalic acid, playing a role in generating structural diversity.

14. Acacic Acid Synthase: This enzyme catalyzes the transformation of cochalic acid into acacic acid, a significant step in the pathway.

15. Gymnemic Acid Synthase: Finally, acacic acid is converted into the bioactive compound gymnemic acid by the action of gymnemic acid synthase, marking the completion of the pathway.

3.2. Biochemistry of Gymnemic Acid Pathway

In order to Support the gymnemic acid biosynthesis it is important to depict the chemical structures of each components which makes it easier in understanding specific chemical transformation in each reaction these reactions is shown in the Fig 2, Fig 3 and Fig 4.

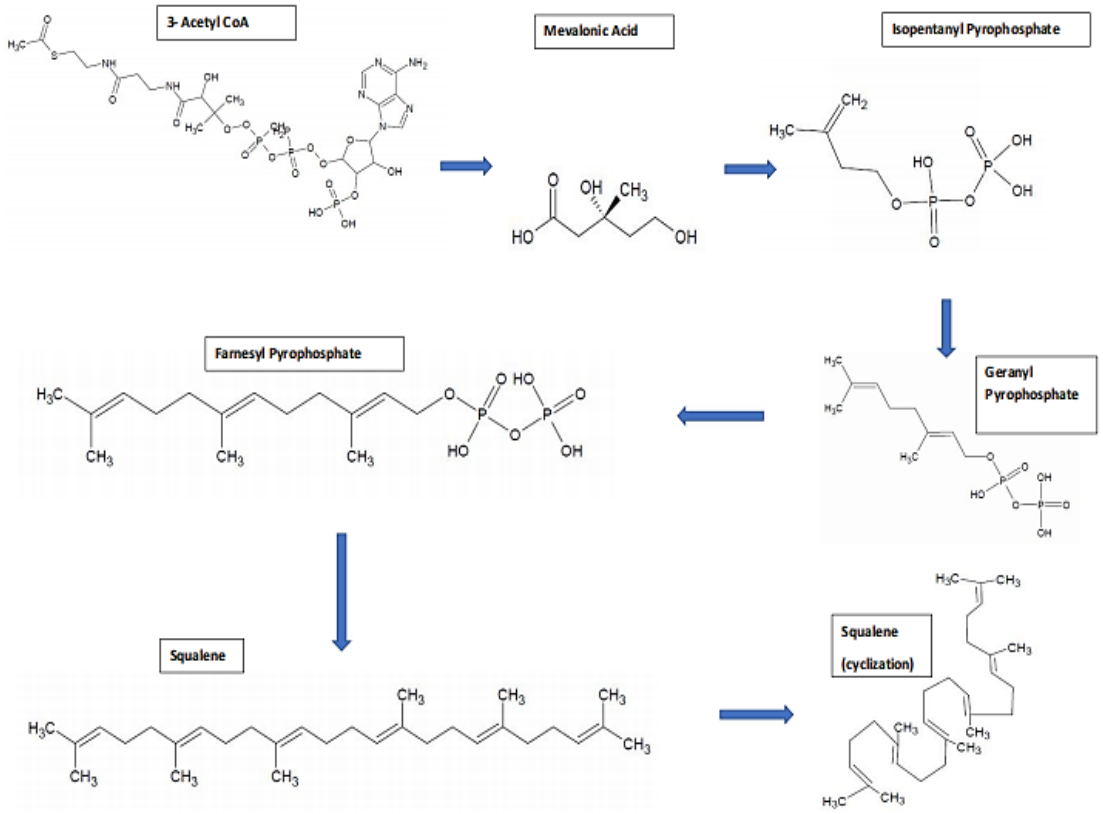

Fig 2: Chemical transformation involved in bio-synthetic pathway starting from acetyl co A till cyclization of Squalene

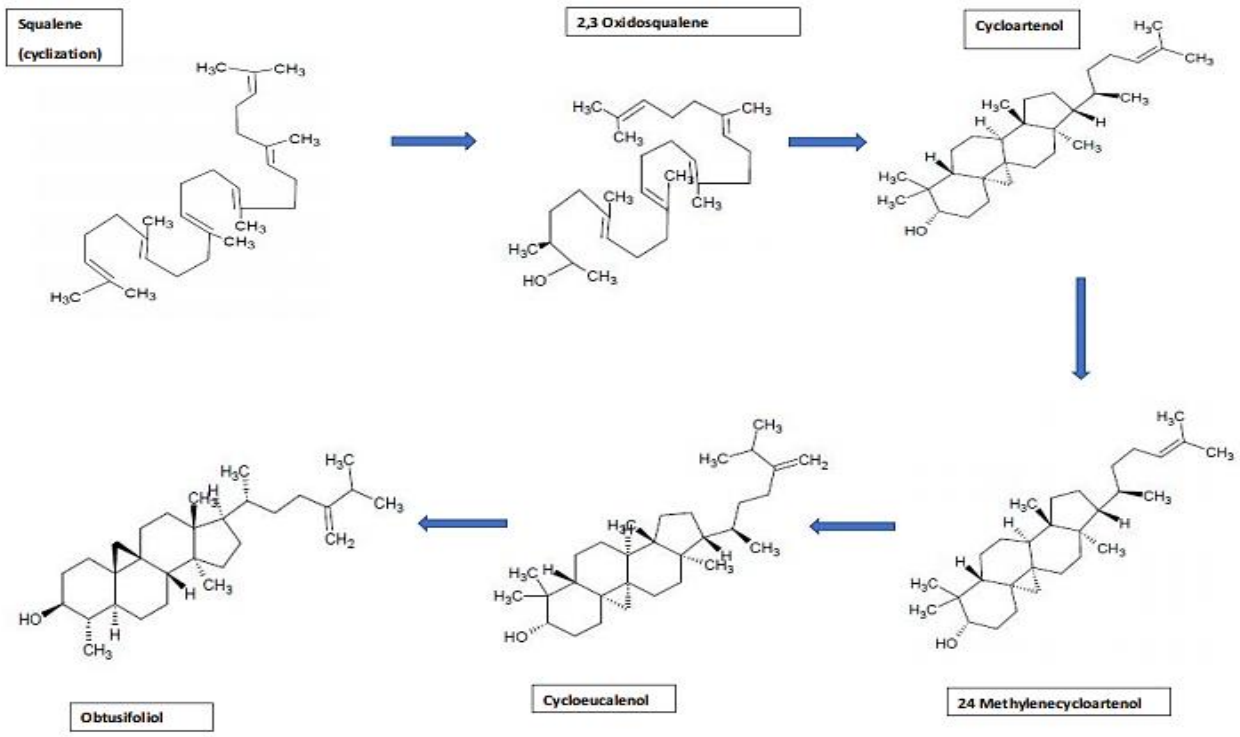

Fig 3: Chemical transformation involved in bio-synthetic reactions from Squalene till Obtusifollol

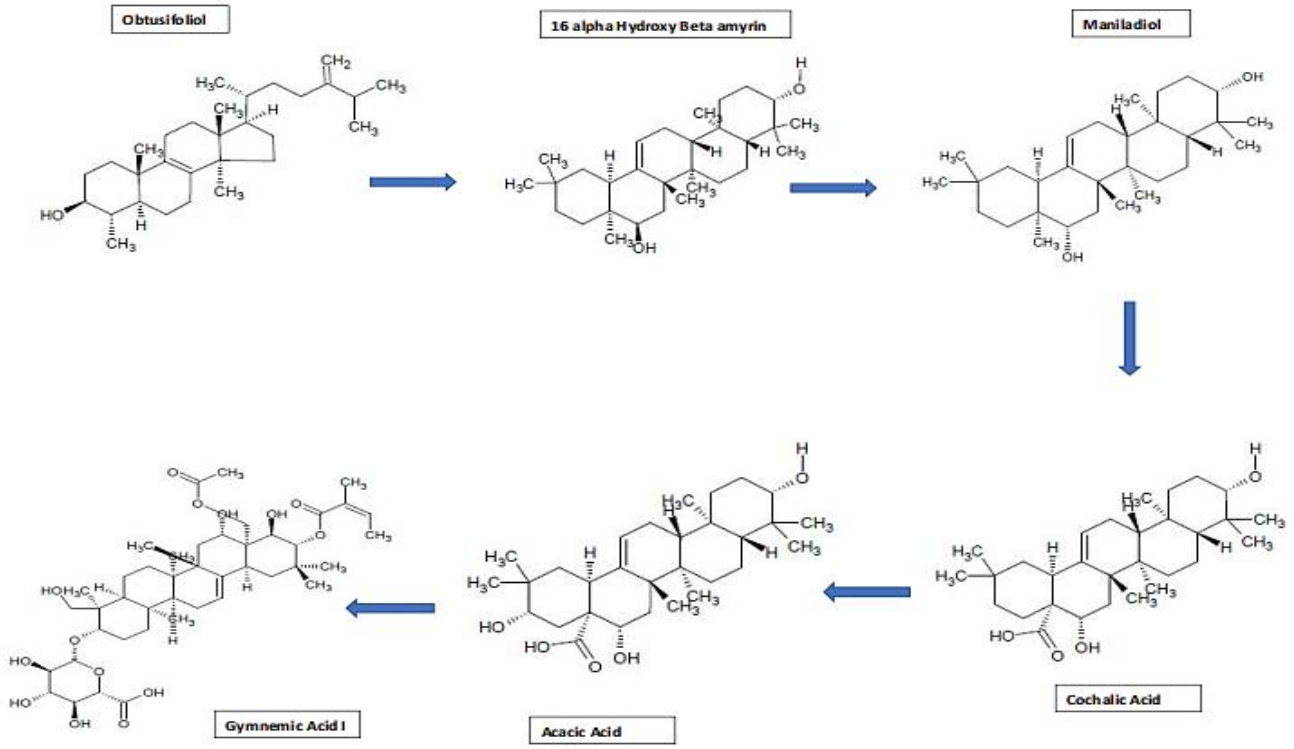

Fig 4: Chemical transformation involved in bio-synthetic reactions from Obtusifollol till Gymnemic acid

4. CONCLUSION

The denovo gymnemic acid biosynthetic pathway involves a coordinated effort by many different enzymes to convert simple precursor molecules into a complex and valuable compound, gymnasium acid. This pathway details the complex molecular transformation of compounds from acetyl Co A to gymnemic acid synthesis, to a biochemical conversion involving 15 enzymes. Moreover, the enzymes required to catalyze the conversion of cochalicic acid to acacic acid and acacic acid to gymnemic acid have not been reported previously. This is the first report identifying these enzymes as Acacic Acid Synthase and Gymnemic Acid Synthase. This pathway not only highlights the complex molecular modifications but also highlights the potential applications of gymnemic acids in various medical contexts. As research continues, *Gymnema sylvestre* holds significant promise as a natural remedy worthy of exploration in the pursuit of better health and well-being.

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