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Systems Biology paves Pathway and Potential Enzymes Predictions towards Anticancer Drug Methyl Jasmonate Biosynthesis

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ABSTRACT

Methyl Jasmonate (MJ) is a potential anticancer drug along with other therapeutic importance. MJ generation is predominantly dependent on plant based route which directly or indirectly interferes with ecosystem and environmental concerns. However, existing microbial platforms are not yet reliable enough to fulfil industrial prospects upon MJ large scale production due to lower productivity, titer and molar yield. To this end, the major objective of this study is to identify an efficient putative metabolic pathway and its corresponding enzyme components following in silico systems biology tools. Main aim of this study is to establish a platform or hypothesis following systems biology which has a great potential to design efficient pathway with corresponding enzymes towards improving MJ biosynthesis in near future. This computational approach helps to design two most promising intermediate metabolic routes of stearic acid to oleic acid biocatalytic conversions considering thermodynamic constraint towards MJ biosynthesis. Furthermore, this in silico combinatorial methodology predicts most energetically favorable downstream bioconversion of oleic acid for MJ biosynthetic circuit design along with novel enzymes identifications. Moreover, the future plan will be to functionalize and validate the entire predicted metabolic pathway through *in vivo* experimentation in suitable chassis microorganisms for ameliorating MJ biosynthesis.

INTRODUCTION

Methyl Jasmonate (MJ) is methyl ester of Jasmonic acid (JA). MJ is a stress responsive secondary regulatory metabolite and distributed ubiquitously in diverse group of plant regimes. The stresses derive either from developmental or environmental signals which up regulates MJ biosynthesis in plants. It executes several cellular regulations in different developmental cascades (growth of root, germination of seeds, ripening of fruits, plant fertility and senescence). MJ serves plant immunity in response to several biotic (insect-driven wounding, pathogens invasions) and abiotic factors (drought, lowering temperature and salinity) (Cheong and Choi, 2003).

MJ has first time been identified from Jasmine flower (*Jasminum grandiflorum*) and rosemary (*Rosmarinus officinalis* L.) and synthesize *de novo* via the Octadecanoid Pathway (OP). Furthermore, MJ structure; OP pathway resemblances to animal anti-inflammatory prostaglandins structure, and its biogenesis respectively (Wasternack and Hause, 2002). JA (MJ precursors) is also biosynthesized from plant pathogenic fungus *Lasiodiplodia theobromae* in 1971 (Aldridge *et al*., 1971). There are several microbial linage exist naturally to produce MJ and/or JA derivatives likely, *Botryodiplodia theobromae* (914.10 mg/L), *Fusarium oxysporum*, *Aspergillus niger*, *Gibberella fujikuroi* (2.5 mg/L), microalga *Schizochytrium mangrovei* (Dhandhukia and Thakkar, 2008; Miersch *et al*., 1999; Miersch *et al*., 1992; Miersch *et al*., 1993; Tsukada *et al*., 2010; Yue and Jiang, 2009). On the other hand, MJ and/or JA derivatives have been extracted from *Jasminium grandiflorum* flowers yielding only 1.25 mg of jasmone concentrate/kg flower, which contains only 0.25% of JA (Dhandhukia and Thakkar, 2007).

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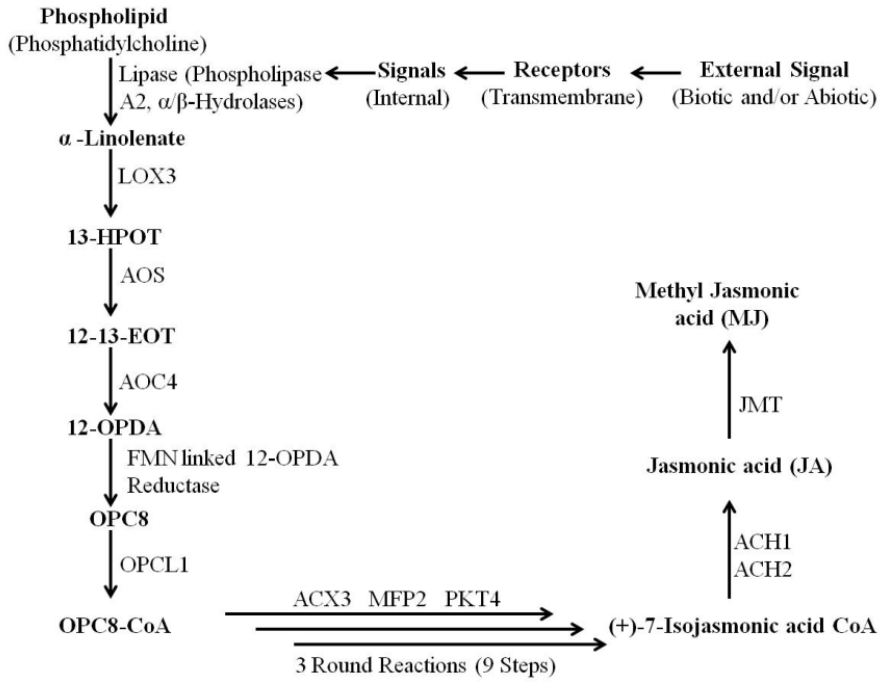

Fig 1: Schematic Diagram of biosynthetic pathway of MJ and/or JA in model plant *Arabidopsis thaliana* (LOX3: Lipoxygenase 3; ASO: Allene oxide synthase; AOC4: Allene oxide cyclase 4; FMN: Flavin mononucleotide; OPCL1: OPC-8:0 CoA ligase 1; 13-HPOT: (9Z,11E,15Z)-(13S)-13-Hydroperoxyoctadeca-9,11,15-trienoic acid; 12-13-EOT: 12-13-(9Z,15Z)-(13S)-12,13-Epoxyoctadeca-9,11,15-trienoic acid); 12-OPDA: (15Z)-12-Oxophyto-10,15-dienoic acid; OPC8: 8-((1R,2R)-3-Oxo-2-{(Z)-pent-2-enyl} cyclopentyl) octanoate; CoA: Coenzyme A; ACX3: Acyl-CoA oxidase 3; MFP2: Enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase; PKT4: Peroxisomal 3-ketoacyl-CoA thiolase 4; ACH: Acyl-CoA Thioesterase; JMT: Jasmonic Acid Carboxyl O-Methyltransferase)

It has clearly been shown that MJ productivity is quiet low in its current state. However, existing microbial platforms are not yet reliable enough to fulfil industrial prospects upon MJ large scale production. Furthermore, MJ and/or JA biosynthesis has also been identified in higher plants likely Arabidopsis, tobacco, tomato and maize (Wasternack, 2007; Wasternack and Hause, 2013; Borrego and Kolomiets, 2016). However, complete biosynthetic pathways are not well characterized considering individual enzymatic reaction steps and all sets of enzymes involve. The *de novo* biosynthetic pathway of MJ and/or JA has been depicted in model plant *Arabidopsis thaliana* where this network is quiet similar with other plants and higher microbes with or without having complete enzymatic reactions and enzyme catalysts (Fig 1). Therefore, it could be a good beginning to focus on this pathway considering individual reaction and enzyme, even though give a trial may be too express and functionalize in an alternative suitable chassis or host microorganisms. But this approach is also being hindered due few bottlenecks at present scenario. Major drawbacks are likely, a. Incredibly longer reaction networks (17 reactions); b. Compartmentalization or different localizations of pathway enzymes (in peroxisome, cytosol, and chloroplast) (Reyes-Díaz *et al*., 2016); c. Unclear cellular regulatory systems and lack of efficient enzymes (Creelman and Mullet, 1997); d. Negative impact of MJ on photosynthesis and autotrophic carbon fixation pathways (i.e. repression of chlorophyll biosynthesis, drastic loss of chlorophyll, Rubisco degradation, increase in respiratory rate; increase in pretease and peroxidase enzyme activities) (Kode, 1992; Parthier, 1990). Moreover, MJ antagonizes the anti-senescence action of kinetin similar to abscisic acid (Ueda and Kato, 1980) in plants. MJ generally has been used as cosmetics, perfume, and flavor industries. But MJ recently paid much attention as therapeutic drug having anticancer activities, antidepressant, anti-aggressive activities, anti-inflammatory activities, anti-nociceptive activities, antiparasitic activities, antimicrobial, and antioxidant activities (increase in L-ascorbic acid or vitamin C biosynthesis) (Pirbalouti *et al*., 2014). Another major driving force for choosing MJ a potential drug compound that it does not cause significant acute toxicity, skin irritation, mucous membrane (eye) irritation, skin sensitization, phototoxicity, and photoallergy upon animal (including human) trials (Rotem *et al*., 2005; Fingrut and Flescher, 2002; Cohen and Flescher, 2009; Flescher, 2005; Umakoro and Abimbola, 2011; Scognamiglio *et al*., 2012). Molecular mechanism and cellular targets of MJ has been shown in great details in cancer therapy (Fig 2) (Cesai *et al*, 2014; Farooqi *et al*., 2012). However, mode of action of MJ for other therapeutic activities mentioned earlier is not pretty much clear yet. Based on this current global scenario, the major objective of this study is to identify an efficient putative metabolic pathway and its corresponding enzyme components following *in-silico* systems biology tools. Main aim of this study is to establish a platform or hypothesis following systems biology which has a great potential to design efficient pathway with corresponding enzymes towards improving MJ biosynthesis in near future.

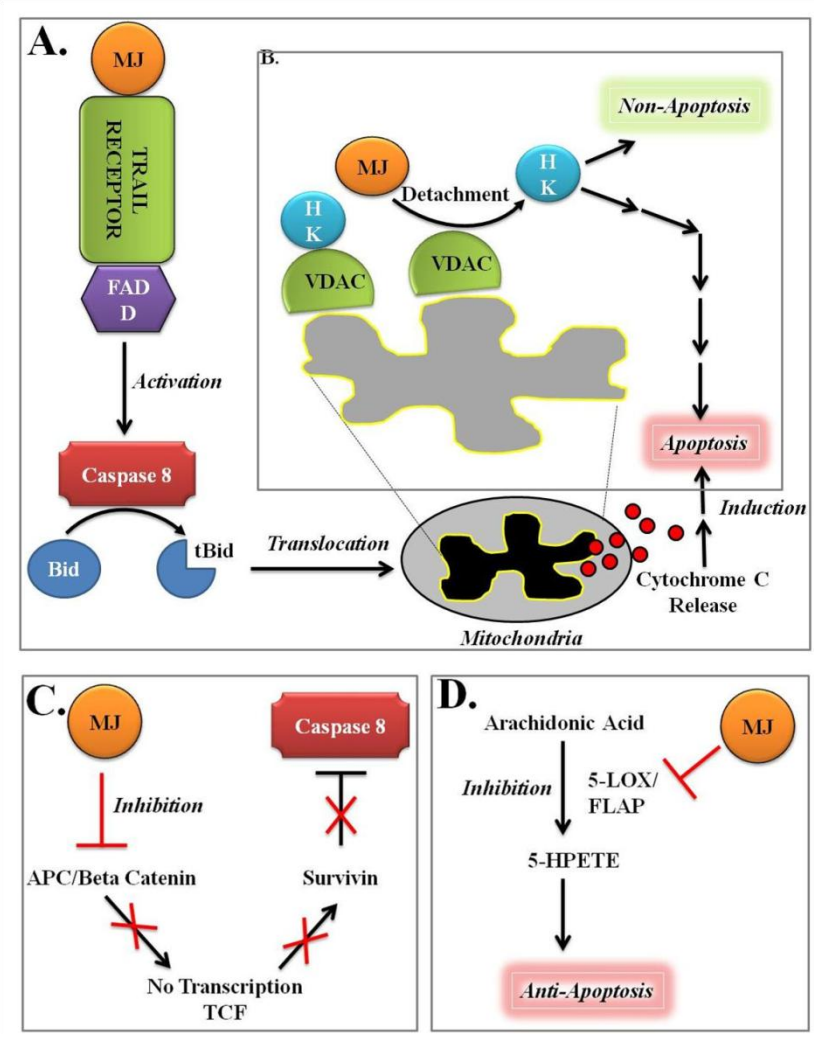

Fig 2: Mode of action of MJ as a potential anticancer drug (VDAC: Voltage-dependent anion channel ; HK: Hexokinase; APC: Antigen presenting cell; Bid: BH3 interacting-domain; tBid: truncated BH3 interacting-domain; FADD: Fas-associated death domain; TRAIL: Tumour necrosis factor-related apoptosis-inducing ligand; TCF: Tumor necrotic factor; 5-LOX: 5-Lipoxygenase; ; FLAP: 5-Lipoxygenase–activating Protein; 5-HPETE: 5-Hydroperoxyeicosatetraenoic acid; ACP: Acyl carrier protein; NADH: Nicotinamide adenine dinucleotide; ΔG: Gibb's free energy change; EC: Enzyme commission; CoA: Coenzyme A**)**

MATERIALS AND METHODS

In this current study, biosynthetic metabolic networks have been designed using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway map, eXTended metabolic space (XTMS) and eEquilibrator systems biology tools. KEGG pathway map represents a high level function of networks of molecular interactions, enzymatic reactions and relations in terms of graphical format. KEGG pathway map tool helps to draw reference pathway maps together with organism specific pathway maps that are computationally generated by matching KEGG Orthology (KO) assignments in the genome with reference pathways. KOs refers to sequence similarity groups as well as functional orthologs. Three major segments i.e. metabolic pathways, gene clusters, and phylogeny has always been considered while defining KOs (Kanehisa *et al*., 2017). XTMS is a rational pathway prediction tools in systems biology which is not only useful for identifying natural as well as for non-natural metabolites and novel enzymatic transformation to design biosynthetic pathways. XTMS approach determines the sets of biomolecular transformations based on specific coding system for derivation of reaction rules for enzymatic reactions, enumeration of all corresponding substrates, intermediates and products. XTMS tool provides an extended metabolic space by providing pathway ranking score, maximum allowable pathway yield and toxicity etc (Carbonell *et al*., 2014). Metabolic Route Explorer (MRE) is another systems biology tool used in this study to suggest foreign enzymes for the biosynthesis pathway design with competing endogenous reactions. It is an effective tool to guide the design and optimization of heterologous biosynthesis pathways providing pathway ranking scores and competing naive reactions. MRE workflow functions considering KEGG databases for biochemical transformations and Boltzmann factor for thermodynamic considerations (Kuwahara *et al*., 2016) within the web based

interface. eQuilibrator is a biochemical thermodynamics calculator for individual enzymatic steps involved within the large metabolic networks. eQuilibrator is effective online systems biology search tool which connects a comprehensive and accurate database of thermodynamic properties of biochemical compounds and enzymatic reactions. It empowers easy Gibb's energies (in Kcal/mol units) calculation of compounds and reactions considering arbitrary pH, ionic strength and metabolite concentrations in an online interactive interface (Flamholz *et al*., 2012). Phylogenetic analysis has been carried out using Phylogeny.fr platform (Dereeper *et al*., 2008) web server (i.e. http://www.phylogeny.fr/) and MEGA5 offline software application (Tamura K *et al*., 2011).

RESULT AND DISCUSSION

In silico design and construction of pathways have been predicted through following simple logistic workflows (Fig 3).

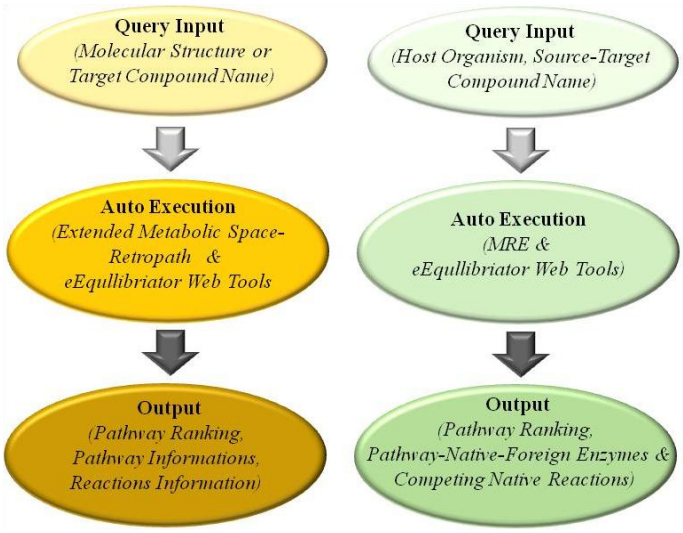

Fig 3: Systems biology (web tool based) workflow towards pathway prediction and design for MJ biosynthesis.

Core of current work flow consists of three major sections; query input, auto execution, and probable outputs. Query input considers few parameters likely host organism, source-target compound name, and molecular structure or target compound name. Secondly, auto execution segment carries out central processing following algorithms based on extended metabolic space-Retropath, MRE, and eEqullibriator web tools. Finally, output comes up with pathway ranking, pathway-reaction informations, pathway-Native-Foreign Enzymes & competing native reactions.

Stearic acid to oleic acid conversion is the first important node of in silico design and construction of this study. In silico design not only provides shortest roots but also providing a very important list of putative enzymes for each an individual enzymatic step including thermodynamic feasibility (i.e. Gibb's free energy change). Stearic acid has been converted into Oleic acid via two nodes likely Coenzyme A (CoA) mediated route and Acyl carrier protein (ACP) mediated route (Fig 4). Stearic acid is one of the predominant chemical constituent of membrane lipids in different microbial regime and higher organisms. Under temperature stress, stearic acid has been naturally conversed into oleic acid through the enzymatic action of desaturase. This phenomenon in fatty acid composition has been extensively investigated in the mesophilic cyanobacteria likely *Anabaena variabilis*, *Synechocystis sp. PCC 6803* and *Anacystis nidulans* (Kiseleva *et al*., 1999). Cyanobacteria carry out this accelerated unsaturation of membrane lipids to maintain the membrane fluidity which is reduced under low temperature conditions.

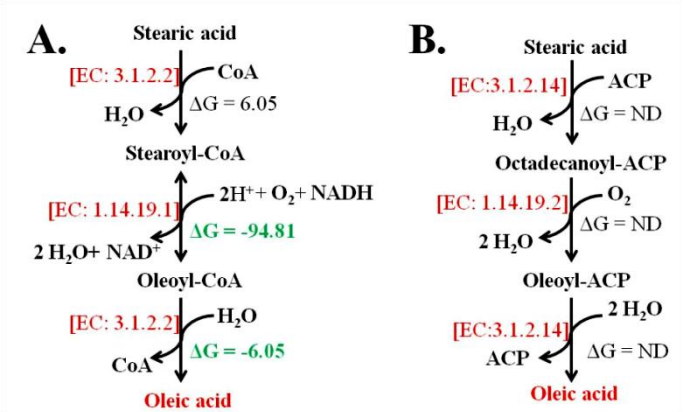

Fig 4: Predicted biosynthetic pathway design for Stearic acid to Oleic acid conversion towards MJ biosynthesis.

In this current study, CoA mediated routes seems more promising having higher negative free energy change value over ACP route. *E.coli* facultative anaerobic bacteria does not carry CoA metabolic route whereas *Arabipsosis thaliana* a plant model follows entire CoA specific route of entry of Stearic acid. While Cyanobacteria (*Synechococcus* sp PCC 7002 and *Synechocystis* sp. PCC 6803) and green algae *Chlamydomonas reinhardtii* bears only second anabolic step excluding other two enzymatic reactions within CoA route. In contrary, facultative anaerobic bacteria (*E.coli*), cyanobacteria (*Synechococcus* sp PCC 7002 and *Synechocystis* sp. PCC 6803) do not carry ACP mediated route. While entire ACP mediated stearic acid to oleic acid conversion route exist in *Chlamydomonas reinhardtii* and *Arabipsosis thaliana.* In ACP route, thermodynamic constraint (i.e. Gibb's free energy change) for all reactions cannot be estimated because some of the compounds don't have an explicit chemical formula. The second segment is "oleic acid to alpha-linolenate biosynthesis". In silico study has been clearly shown that this segment is slightly energetically unfavorable but several enzyme classes are involved which could be tried out under wet laboratory experimental trial towards screening potential enzymes (Fig 5). In the third phase, alpha linolenic acid has been converted into 3-oxo-2-(cis-2'-pentenyl)-cyclopentane-1-octanoate (OPC8). In this segment, most of enzymatic steps are thermodynamically favorable excluding (15Z)-12-Oxophyto-10, 15-dienoic acid (12-OPDA) to OPC8 conversion (Fig 5).

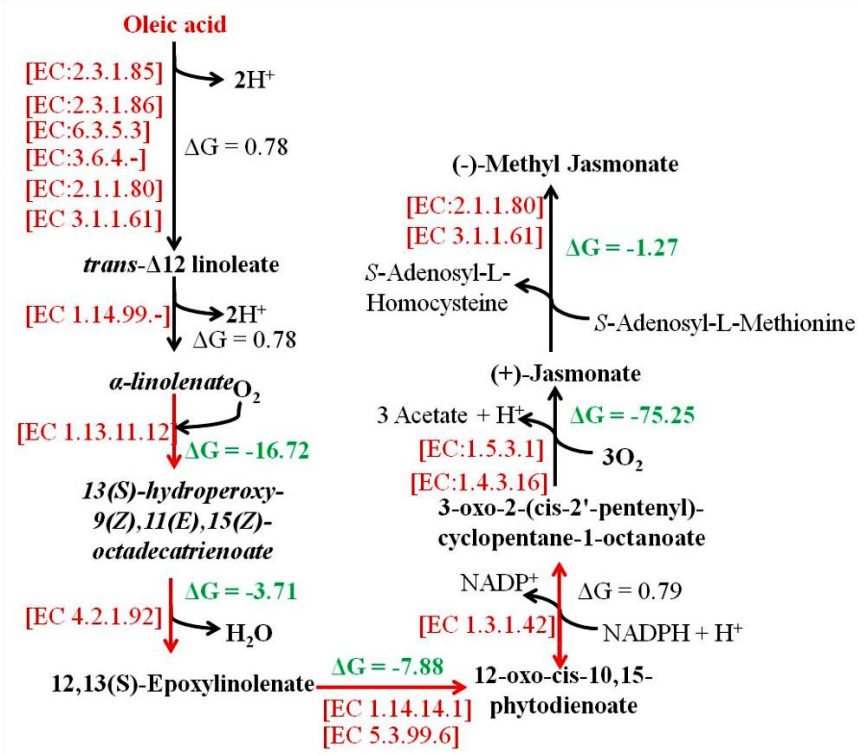

Fig 5: Predicted biosynthetic pathway design for MJ biosynthesis from stearic acid including thermodynamic constraints and putative enzyme classes.

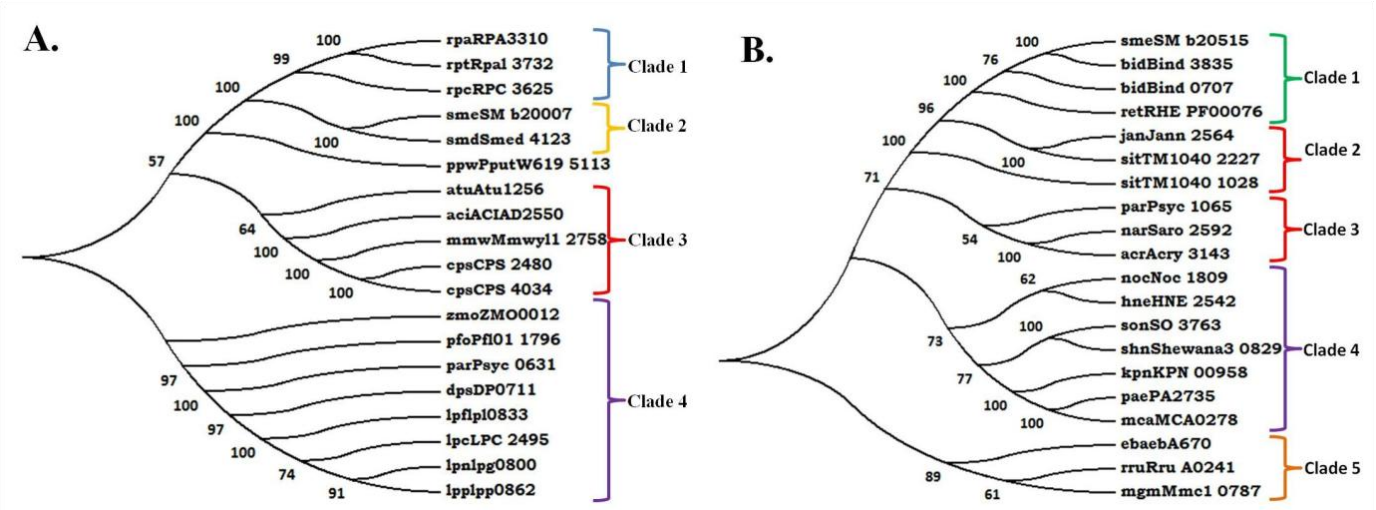

Fig 6: Phylogenetic analysis of novel enzymes involved in final two steps including (A). 3-oxo-2-(cis-2'-pentenyl)-cyclopentane-1-octanoate to JA and (B). JA to MJ conversions based on 1000 Bootstrapping and Neighbor-Joining method **(**aciACIAD2550: *Acinetobacter* sp. Sarcosine oxidase/Oxidoreductase; parPsyc_0631: *Psychrobacter arcticus* L-Aspartate oxidase; mmwMmwyl1_2758: *Marinomonas* sp. Sarcosine oxidase/Oxidoreductase; pfoPfl01_1796: *Pseudomonas fluorescens* putative xanthine dehydrogenase; lpcLPC_2495: *Legionella pneumophila* L-Aspartate oxidase; lpnlpg0800: *Legionella pneumophila* L-Aspartate oxidase; lpplpp0862: *Legionella pneumophila* L-Aspartate oxidase; lpflpl0833: *Legionella pneumophila* L-Aspartate oxidase; dpsDP0711: *Desulfotalea psychrophila* L-Aspartate oxidase; rpcRPC_3625: *Rhodopseudomonas palustris* Catalase; smeSM_b20007: *Sinorhizobium meliloti* Catalase; smdSmed_4123: *Sinorhizobium medicae* Catalase; cpsCPS_2480: *Colwellia psychrerythraea* Sarcosine Oxidase; cpsCPS_4034:*Colwellia psychrerythraea* Sarcosine Oxidase; ppwPputW619_5113: *Pseudomonas putida* Catalase; zmoZMO0012: *Zymomonas mobilis* oxygen-independent coproporphyrinogen III oxidase; rpaRPA3310: *Rhodopseudomonas palustris* Catalase; rptRpal_3732: *Rhodopseudomonas palustris* Catalase; atuAtu1256: *Agrobacterium fabrum* Cytochrome P450 hydroxylase/monooxygenase; smeSM_b20515: *Sinorhizobium meliloti* Methyltransferase; retRHE_PF00076: *Rhizobium etli* Methyltransferase; sitTM1040_1028: *Ruegeria* sp. histidine kinase; bidBind_0707: *Beijerinckia indica* methyltransferase/methylesterase; bidBind_3835: *Beijerinckia indica* methyltransferase/methylesterase; ebaebA670: *Aromatoleum aromaticum* adenine-specific DNA-methyltransferase; janJann_2564: *Jannaschia* sp. methyltransferase/methylesterase; paePA2735: *Pseudomonas aeruginosa* Methyltransferases; sitTM1040_2227: *Ruegeria* sp. Methyltransferase; mcaMCA0278: *Methylococcus capsulatus* methyltransferase; nocNoc_1809: *Nitrosococcus oceani* methyltransferase; parPsyc_1065: *Psychrobacter arcticus* uroporphyrinogen-III C-methyltransferase; rruRru_A0241: *Rhodospirillum rubrum* Methyltransferase; narSaro_2592: *Novosphingobium aromaticivorans* Methyltransferase; acrAcry_3143: *Acidiphilium cryptum* Cyclopropane-fatty-acyl-phospholipid synthase; mgmMmc1_0787: *Magnetococcus marinus* Methyltransferase; kpnKPN_00958: *Klebsiella pneumoniae* Methylase; sonSO_3763: *Shewanella oneidensis* Spermidine synthase; hneHNE_2542: *Hyphomonas neptunium* Methyltransferase; shnShewana3_0829: *Shewanella* sp. spermidine synthase).

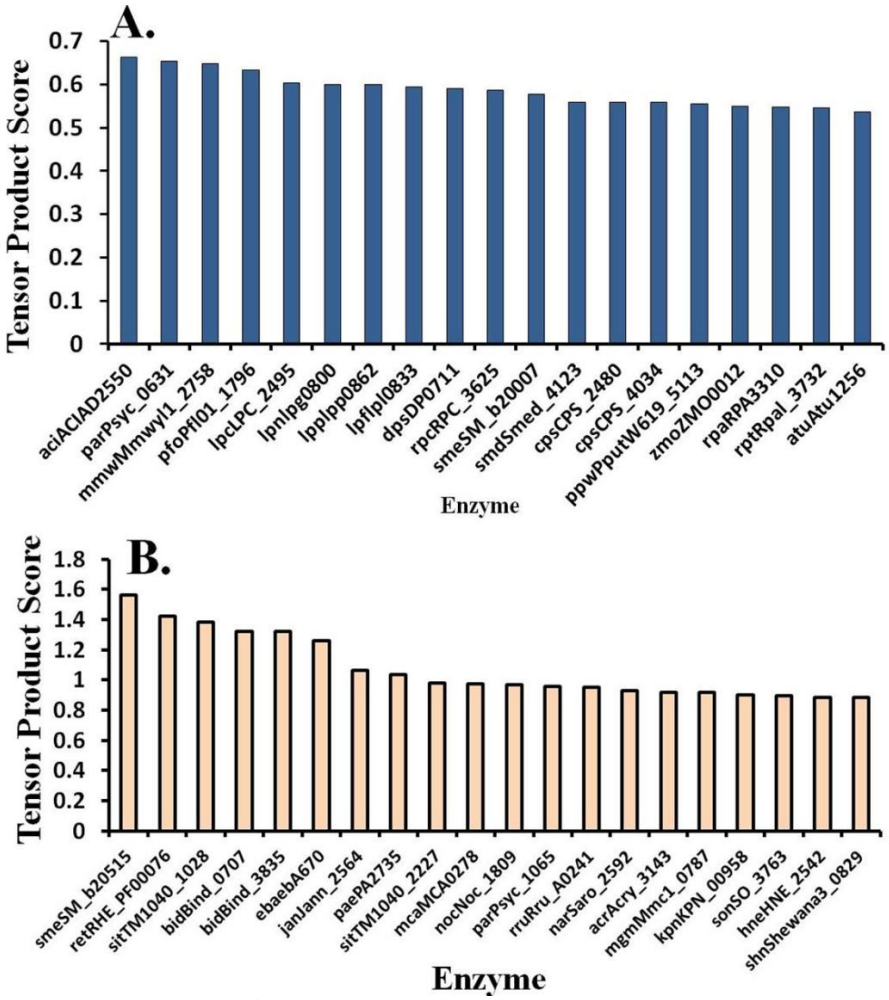

Fig 7: Biocatalytic efficacy of novel enzymes involved in final two steps including (A). 3-oxo-2-(cis-2'-pentenyl)-cyclopentane-1-octanoate to JA and (B). JA to MJ conversions based on tensor product score.

In *Arabipsosis thaliana* and in few higher plants, OPC8 to MJ and/or JA catalytic conversion requires 12 additional steps. Additionally, unavailability and/or inefficient catalytic activity of Jasmonic Acid Carboxyl O-Methyltransferase (JMT) enzyme restrict industrial production of JA via microbial route in comparison to plant based production. To this end, in silico design has shown that *de novo* MJ synthesis can be bypassed from OPC8 to MJ considering two most vital novel enzymatic steps (Fig. 5). These two enzymatic steps include OPC8 to (+)-JA and (+)-JA to MJ bioconversions. Furthermore, these two enzymatic steps are highly energetically favorable. Different potential enzymes involved in these reactions are classified into different groups based on phylogenetic analysis (Fig 6) and their probabilistic biocatalytic efficacy has been depicted in terms of Tensor product score (Fig 7) (Carbonell and Faulon, 2010; Faulon *et al*., 2008).

CONCLUSION

Synthetic Biology and Systems Biology combinatorial approach is the Holy Grail towards novel drug discovery and design of its biosynthetic pathway inside small microbial bugs (Ghosh, 2016). In over all, the current study is very strong evidence that pathway prediction and designing systems biology tools can reduce time for experimentation (i.e. trial and error conventional approach for pathway design), expenses of research, and manual effort time to time. It not only provides novel biosynthetic steps but also provides information on novel putative enzymes. In this study, predicted and designed synthetic metabolic pathways for MJ biosynthesis from stearic acid seems promising, though this entire metabolic pathway functionalization needs to be validated through *in vivo* experimentation in suitable chassis microorganisms (*Escherichia coli*, *Synechococcus* sp. PCC 7002, *Synechococcus elongatus* PCC 7942, *Synechococcus* sp. PCC 6803 and *Chlamydomonas reinhardtii*) towards industrialization via microbial biosynthetic route. Current systems biology pathway prediction and design tools in its current state could be ameliorated by connecting enzyme promiscuity and enzyme regulations phenomena in near future. However, this combinatorial methodologies could also be implemented to design novel metabolic circuits of other high value added biochemicals

generations likely antimalarial drug Artemisinin and cholesterol lower drug 1,2,4 butanetriol. Furthermore, in silico approach enforces critical decisive role at very initial stage to define if the targeted biomolecules ought to be chosen towards further studies or not.

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