
**UNIVERSITI PUTRA MALAYSIA**

# *AGROBACTERIUM RHIZOGENES-MEDIATED HAIRY ROOT OF APPLE OF SODOM (SOLANUM MAMMOSUM L.) FOR OPTIMIZED PRODUCTION OF SOLASODINE*

***OOI CHAI THEAM***

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**By**

**OOI CHAI THEAM**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, In Fulfillment of the Requirements for the Degree of Doctor of Philosophy**

**January 2015**

DEDICATED TO:

**FATHER, MOTHER AND BROTHER**

WHO ALWAYS HAVE FAITH IN ME

AND

THEIR SUPPORT HAS GUIDED ME TO GO THROUGH

ALL THE OBSTACLES IN LIFE

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the Degree of Doctor of Philosophy

**_AGROBACTERIUM RHIZOGENES_-MEDIATED HAIRY ROOT OF APPLE OF SODOM (_SOLANUM MAMMOSUM_ L.) FOR OPTIMIZED PRODUCTION OF SOLASODINE**

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**OOI CHAI THEAM**

**January 2015**

**Chairman: Professor Maziah Mahmood, PhD**

**Institute: Institute of BioScience**

The increasing demand of diosgenin for high-revenue synthesis of useful steroid hormones such as progesterone and cortisone by the pharmaceutical industries has driven researchers to look for other alternatives to replace this compound in order to prevent the increase of price of the end products. The aglycone of the steroidal alkaloid, solasodine, which was reported to be present in *Solanum mammosum*, can replace diosgenin and be converted to 16-dehydropregnenolone, which is a key intermediate in the synthesis of steroid hormones. In order to produce more solasodine from *S. mammosum* in a shorter period of time, hairy root culture mediated by *Agrobacterium rhizogenes* was established in this study. Besides that, the production of solasodine from transformed hairy culture of *S. mammosum* has not been reported previously. In order to increase the number of transformants to enable a wider selection of better transformants which were highly productive both in terms of biomass growth as well as the production of secondary metabolites of interest, optimization of the protocol for hairy root induction using five different strains of *A. rhizogenes*, that are, strain ATCC31798, ATCC43057, AR12, A4 and A13, on the leaf explants of *S. mammosum* has been carried out in the present study. Furthermore, in order to enhance the production of solasodine, the culture conditions of the transformed hairy root cultures were optimized through medium manipulation, elicitation and precursor feeding. The results showed that by adding 300 µM methyl jasmonate, 100 µM cholesterol, and 1000 µM L-arginine into the culture medium (liquid modified MS medium with ammonium to nitrate ratio of 10.3 mM : 39.4 mM and 4 % (w/v) sucrose) at day 20 of the culture could improve the solasodine content in both the hairy root line-ATCC31798 and line-A4 induced by *A. rhizogenes* strain ATCC31798 and A4 respectively. The solasodine productivity for hairy root line-ATCC31798 was 4.44 ± 0.42 mg/g dry weight roots and line-A4 was 4.55 ± 0.42 mg/g dry weight roots with a total biomass of 188.7 ± 21.7 mg and 176.7 ± 23.4 mg respectively on dry weight basis after 32 days of culture under 16-hour light / 8-hour dark regime, when using 50 mg fresh weight roots as initial inoculum size. The solasodine

yield for both hairy root lines was at least nine times higher than those before any optimization. The improved solasodine production while maintaining a relatively high biomass yield could reduce the cost for steroid synthesis in the pharmaceutical industry in the long run.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**AKAR RERAMBUT *AGROBACTERIUM RHIZOGENES*-PENGANTARA UNTUK TERUNG SUSU KAMBING (*SOLANUM MAMMOSUM* L.) BAGI PENGHASILAN SOLASODINE YANG OPTIMUN**

Oleh

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Peningkatan keperluan terhadap diosgenin untuk sintesis hormon steroid yang dapat membawa keuntungan yang lumayan oleh industri-industri farmaseutikal telah menggalakkan para penyelidik untuk mancari alternatif bagi menggantikan kompaun ini supaya dapat mengelakkan kenaikan harga kepada produk-produk steroid. Aglikon untuk alkaloid steroid, solasodine, yang dilaporkan terdapat di dalam *Solanum mammosum*, boleh menggantikan diosgenin dan ditukarkan kepada 16-dehydropregnenolone, iaitu satu pengantara yang penting dalam sintesis hormon steroid. Bagi menghasilkan lebih banyak solasodine daripada *S. mammosum* dalam masa yang singkat, kultur akar rerambut melalui pengantara *Agrobacterium rhizogenes* telah dilaksanakan dalam kajian ini. Selain itu, penghasilan solasodine daripada kultur akar rerambut *S. mammosum* tidak pernah dilaporkan sebelum itu. Dalam usaha untuk meningkatkan bilangan transformants bagi memberi pilihan yang lebih luas terhadap transformants yang lebih baik dan lebih produktif dari segi pertumbuhan biomas dan juga pengeluaran metabolit sekunder, pengoptimuman protokol untuk induksi akar rerambut dengan menggunakan lima strain *Agrobacterium rhizogenes* yang berbeza, iaitu, strain ATCC31798, ATCC43057, AR12, A4 and A13, terhadap eksplan-eksplan daun *S. mammosum* telah dijalankan. Tambahan pula, keadaan-keadaan kultur akar rerambut telah dioptimunkan melalui penggubahan medium, elisitasi dan penambahan prekursor ke dalam medium kultur bagi meningkatkan penghasilan solasodine. Keputusan menunjukkan bahawa penambahan 300 µM metil jasmonate, 100 µM kolesterol, dan 1000 µM L-arginine ke dalam medium kultur (medium MS cecair yang telah diubahsuai dengan kandungan ammonium dan nitrate bernisbah 10.3 mM : 39.4 mM dan 4 % (w/v) sukrosa) pada hari ke-20 semasa eksperimen dijalankan dapat meningkatkan kandungan solasodine di dalam akar rerambut *line*-ATCC31798 dan *line*-A4 yang diinduksikan oleh *A. rhizogenes* strain ATCC31798 dan A4 masing-masing. Produktiviti solasodine untuk akar rerambut *line*-ATCC31798 adalah sebanyak 4.44 ± 0.42 mg/g berat kering akar dan *line*-A4 adalah sebanyak 4.55 ± 0.42 mg/g berat kering akar

dengan jumlah biomas 188.7 ± 21.7 mg dan 176.7 ± 23.4 mg masing-masing dalam berat kering selepas 32 hari kultur di bawah 16 jam terang / 8 jam gelap rejim, apabila 50 mg berat segar akar digunakan sebagai saiz inokulum asal. Hasil solasodine untuk kedua-dua *line* akar rerambut adalah sekurang-kurangnya sembilan kali ganda lebih tinggi berbanding dengan kandungannya di dalam akar-akar rerambut sebelum pengoptimuman. Peningkatan penghasilan solasodine di samping mengekalkan pengeluaran biomas yang tinggi dapat mengurangkan kos untuk sintesis steroid dalam industri farmaseutikal dalam jangka masa panjang.

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I certify that a Thesis Examination Committee has met on 12th January 2015 to conduct the final examination of Ooi Chai Theam on his thesis entitled "*Agrobacterium rhizogenes*-mediated hairy root of Apple of Sodom (*Solanum mammosum* L.) for optimized production of solasodine" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15th March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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| | |
|---|---|
| AS | acetosyringone |
| ATCC | American Type Culture Collection |
| bp | base pair |
| cm | centimeter |
| $^{o}$C | degree Celsius |
| DAD | diode array detection |
| dw | dry weight |
| fw | fresh weight |
| g | gram |
| h | hour |
| HPLC | high-performance liquid chromatography |
| LB | Luria-Bertani |
| m | meter |
| min | minute |
| mg | milligram |
| ml | milliliter |
| mm | millimeter |
| mM | millimolar |
| µm | micrometer |
| µl | microliter |
| µg | microgram |
| µM | micromolar |
| M | molar |

| | |
|---|---|
| MS | Murashige and Skoog |
| ng | nanogram |
| nm | nanometer |
| nm | nanometer |
| % (v/v) | percent (volume/volume) |
| % (w/v) | percent (weight/volume) |
| PDA | photodiode array detector |
| *rol* | root loci |
| rpm | revolution per minute |
| TLC | thin-layer chromatography |
| UV | ultraviolet |
| V | volt |

# CHAPTER 1

## INTRODUCTION

Plants as producers in the first trophic level in the ecosystem have privileged access to the energy through photosynthesis. They can afford to synthesize a wide spectrum of exotic chemical compounds to aid their survival. There are approximately 300,000 documented species of higher plants on this planet with more than 200,000 individual natural products have been identified from them till date (Wu and Chappell, 2008). These natural products can be further divided into primary and secondary metabolites. Primary metabolites are the constituents essential for all living cell types, while secondary metabolites are structurally and chemically more diverse than the primary metabolites and they outnumber the latter by orders of magnitude (Lattanzio, 2013). Many of the secondary metabolites derived from plants are economically important pharmaceuticals, agrochemicals, cosmetics, fine chemicals and nutraceuticals (McChesney et al., 2007). Because of the chemical and functional diversity of these secondary metabolites, they acquire strong physiological activities, and thus they have been used by human to treat a variety of ailments (Chaudhuri et al., 2009).

Despite the progress made in the organic synthesis or semi-synthesis of a wide range of compounds that are similar to those produced by the plants, the extraction of secondary metabolites from the plants is still of considerable commercial importance (Namdeo, 2007). Namdeo (2007) further described that a large number of these metabolites are difficult or virtually impossible to synthesize at economic values; and in several cases, natural product is easily accepted by the public than an artificial product. Unfortunately, the extraction of natural products could suffer from a variety of serious problems including low levels of productivity and heterogeneous quality over very long growth periods, cost- and labour-intensive because of the purification of desired compound requires separation from a multitude of other compounds of similar structure, and the yields are subjected to regional and environmental factors (Baldi et al., 2007).

The evolving of commercially important secondary metabolites has thus led to a great interest in the plant secondary metabolism, particularly in the possibility to alter the production of bioactive metabolites by means of tissue culture technology in the recent years (Hussain et al., 2012). Plant cell and tissue cultures have been established routinely under sterile conditions from the explants, such as plant leaves, stems, roots and meristems, for multiplication and extraction of the secondary metabolites. Therefore, it is an attractive alternative to the extraction of whole plant material. The principle advantage of this technology is that it may offer a continuous and reliable source of plant pharmaceuticals, and thus it could be used for large scale culture from which the metabolites of interest could be extracted (Irem, 2012).

The *in vitro* production of secondary metabolites in the hairy root culture by applying *Agrobacterium rhizogenes*-mediated genetic transformation as a stable

source of biologically active chemicals has been given great attention by researchers in the past few decades (Guillon et al., 2008). In this study, hairy roots have been induced from the *in vitro* cultures of *Solanum mammosum* with the help of five different strains of *A. rhizogenes*. This plant was chosen mainly because the hairy root culture of this species has not been reported scientifically except the establishment of callus described by Indrayanto and Sutarjadi (1986). Although the most recent publication on phytochemical analysis of field-grown *S. mammosum* by Telek et al. (1977) showed that this species contained steroidal alkaloid solasodine and its corresponding glycoalkaloids, these compounds were absent from the callus culture as reported by Indrayanto and Sutarjadi (1986), which may be due to the nature of dedifferentiated cells. Jacob and Malpathak (2005) and Pawar et al. (2008), on the other hand, showed that the hairy root cultures of both *S. khasianum* and *S. surattense* were able to produce a considerable amount of solasodine.

Solasodine has been noted by Dewick (2009) that it is able to replace diosgenin to be converted to 16-dehydropregnenolone, a key intermediate in the synthesis of high-revenue steroidal drugs such as progesterone and cortisone in the pharmaceutical industries The transformed hairy roots have been reviewed by Sheludko and Gerasymenko (2013) to be able to grow relatively fast in the hormone-free medium, genetically and biochemically stable, and synthesize organogenesis-associated metabolites, which these features are hardly found in the callus and cell cultures. Hence, the transformed hairy roots could be potentially used to produce more solasodine to cater the increasing demand for intermediates by the pharmaceutical industries for steroid synthesis.

Although it is clear that the hairy roots produced from *A. rhizogenes*-mediated genetic transformation could generate more biomass as compared with the non-transformed roots when using the same culture conditions, the level of secondary metabolite of interest (solasodine) needs to be determined. Thus, optimizing the hairy root cultures may increase the production of solasodine. In addition to changing the inorganic composition of the culture medium, the addition of elicitors and precursors may also enhance the potential of hairy roots in synthesizing solasodine as those being demonstrated by Indrayanto et al. (1995) on the shoot culture of *S. laciniatum* and and also by Lee et al. (2007) on the cell culture of *S. lyratum*. Therefore, the objectives of this study were:

1. to establish and optimize *A. rhizogenes*-mediated genetic transformation on *S. mammosum*
2. to establish the hairy root cultures for the production of solasodine
3. to enhance the production of solasodine through optimization of the culture conditions
4. to enhance the production of solasodine by elicitation and precursor feeding.

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