Advantages from two world in one flask

Hiromichi Minami*, Ju-Sung Kim*, Nobuhiro Ikezawa†, Tomoya Takemura†, Takane Katayama*, Hidehiko Kumagai*, and Fumihiko Sato Microbial production of plant benzylisoquinoline alkaloids

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- background
- result
- conclusion
- reference
Alkaloids
- low-molecular-weight, nitrogen-containing
- benzylisoquinoline alkaloids produced via (S)- reticuline from tyrosine
- development of antimalarial and anticancer drugs\textsuperscript{[1]}
- difficult to produce in plants, too complex for cost-effective
- useful as novel medicines. (aporphine type alkaloid magnoflorine protect HDL)\textsuperscript{[2-4]}
The combination of microbial and plant-derived genes in microbial systems\[^8\] leads to enzymatic synthesis. This process involves chemically synthesized\[^5\] transgenic opium poppy plants\[^6\].
difficult to reconstruct for the efficient production of divergent benzylisoquinoline alkaloids\[9\]
construction of E. coli expression vectors for reticuline production

( expression vector of MAO and NCS)

monoamine oxidase (MAO)
norcoclaurine synthase (NCS)
norcoclaurine 6-O-methyltransferase (6OMT)
coclaurine-N-methyltransferase (CNMT)
3-hydroxy-N- methylcoclaurine-4-O-methyltransferase (4 OMT)
expression vector of 6OMT, CNMT, and 4 OMT
first step (Escherichia coli)

NCS (norcoclaune synthase, C. japonica cells)\[11\]
- CjNCS1
- CjPR10A
second step (Saccharomyces cerevisiae)\cite{12}

Berberine bridge enzyme (BBE)

CYP80G2

Corytuberine-N-methyltransferase (CNMT?)

Magnoflorine

(S)-3'-Hydroxy-N-methylcoclaurine
culture media of transgenic E. coli \textsuperscript{[13, 14]}

Culture media of transgenic E. coli with empty vectors (left) and reticuline biosynthetic genes (right)
reticuline production in E. coli.
difference between in vivo and in vitro production

in vivo production

in vitro production
biosynthesis of intermediates in a benzylisoquinoline alkaloid pathway [15]
CID mass spectrum for norlaudanosoline (A), reaction product in (B), 3'-hydroxycoclaurine (C), reaction product in (D)
CID mass spectrum of 3'-hydroxy-N'-methylcoclaurine (E), reaction product in (F), norreticuline (G), and reaction product in (H)
benzylisoquinoline alkaloid production in microbes
(magnoflorine production)
CID mass spectrum for magnoflorine (A), reaction product in (B)
(S)- Scoulerine production in microbial
CID mass spectrum for scoulerine (C), and reaction product in (D)
success in ways for giving microbial cells the ability to produce plant alkaloid
- provide a variety of isoquinoline alkaloid skeletons
- further progress with microbial systems for use in the pharmaceutical industry \cite{16, 17}
- a novel basic tool for manufacturing a broad range of plant-derived metabolites, particularly isoquinoline alkaloids.


thanks for your patience
welcome questions