Curr. Issues Mol. Biol. 11 (Suppl. 1) i35–45. Online journal at www.cimb.org

An Account of Cloned Genes of Methyl-erythritol-4-phosphate Pathway of Isoprenoid Biosynthesis in Plants

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Received 8 August 2008
Revised 19 September 2008
Accepted 23 October 2008

Abstract:

Isoprenoids, also known as terpenoids, are biosynthesized by the condensation of the two C_5 unit isopentenyl diphosphate (IPP) and isomer dimethylallyl diphosphate (DMAPP). Generally, plants use two separate pathways plastidial Methyl-erythritol-4-phosphate (MEP) and cytosolic acetate-mevalonate (MVA) pathways for formation of IPP. The genes, enzymes and intermediates of the MEP pathway have been unravelled in plants over the past few years. Interestingly, MEP pathway enzymes are encoded by nuclear genes but they function in plastids to produce precursors for isoprenes, monoterpenes, carotenoids, abscisic acid, gibberellins, and the side chain of chlorophylls, tocopherols, phylloquinones, and plastoquinone. In *Arabidopsis thaliana*, a complete set of genes of MEP pathway homologous to the *E. coli* MEP pathway genes have been identified. Although, these genes have been cloned and characterized from several other plants but overall information about them at one place is not available so far. Though, a range of reviews are available about their roles in isoprenoid biosynthesis and regulation. Therefore, we decided to compile the data on cloned and characterized genes of MEP pathway in plants. Also, we summarize the results of the previously published reports, particularly those which were based on incorporation of ^{13}C-glucose or by application of specific inhibitors such as mevinolin and fosmidomycin to look into the MEP pathway in plants. In addition, we searched for the two key enzymes DXS and HMGR that could be assigned for the acetate-MVA and MEP pathway with the help of bioinformatics tools. Presence or absence of these enzymes can be correlated with respective isoprenoid biosynthetic pathways in plants.

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Keywords: Isoprenoids; Methyl-erythritol-4-phosphate (MEP); Acetate-MVA pathway; Hydroxyl-methylglutaryl-CoA reductase (HMGR); 1-deoxy-D-xylulose 5-phosphate synthase (DXPS or DXS).

Introduction

Plant secondary metabolites *viz.*, isoprenoids have always been fascinating for the researchers. Obviously, they are the largest and most diverse class of plant secondary metabolites (Dubey *et al*., 2003). Over the years isoprenoids have been exhaustively investigated. There are many research papers, reviews, commentaries and books are available covering various aspects of isoprenoids *viz.*, biosynthesis and regulation and functions in plants and microorganisms (Croteau, 1987; Rohmer, 1999; 2003; Lichtenthaler, 1999; Lichtenthaler, 2001; Eisenreich *et al*., 1997; 2001; 2004; Rodrıguez-Concepcion and Boronat, 2002; Chemler *et al*., 2006; Cheng *et al*., 2007). Isoprenoids are multifunctional; they play very important roles in membrane structure, redox reactions, light harvesting and photo-protection, and regulations of growth and development. They not only perform various roles in the plant's life such as, plant-environment, plant–insect, plant–microorganism and plant–plant interactions but they became an essential part of our life as medicines, flavours, fragrances, cosmetics, dyes, insecticides and more (Verpoorte *et al*., 2002; Harborne, 2001; Dixon, 2001). Currently, isoprenoids are being used as anti-cancer and antimicrobial drugs for example artimicinin as a powerful antimalarial (Dhingra *et al*., 2000) and taxol as anti-cancer (Cragg *et al*., 1997) agents.

Despite the great deal of structural and functional diversity all isoprenoids are synthesized by consecutive condensation of common C_5 isoprene precursor; isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). IPP therefore is regarded as the universal precursor of all the isoprenoids. IPP, in turn is biosynthesized in two different sites *via* two separate and independent biochemical pathways: 1. Cytosolic acetate-MVA pathway and 2. Plastidial Methylerythritol 4- phosphate (MEP) also called as 1-deoxy-D-xylulose 5-phosphate (DOXP) or glyceraldehyde-3-phosphate-pyruvate (GAP-Pyruvate) pathway (Fig. 1). In the present article, the pathway is described as MEP pathway. In general, acetate-MVA pathway produces sesquiterpenes and triterpenes while MEP pathway produces monoterpenes, sesquiterpenes, diterpenes, tetraterpenes, plastoquinone and prenyl side chains of chlorophyll.

In brief, MEP pathway (Fig. 1) begins with the formation of 1-deoxy-D-xylulose 5-phosphate (DOXP/DXP) by the condensation of pyruvate and glyceraldehyde 3-phosphate catalysed by DOXP synthase (DXS,

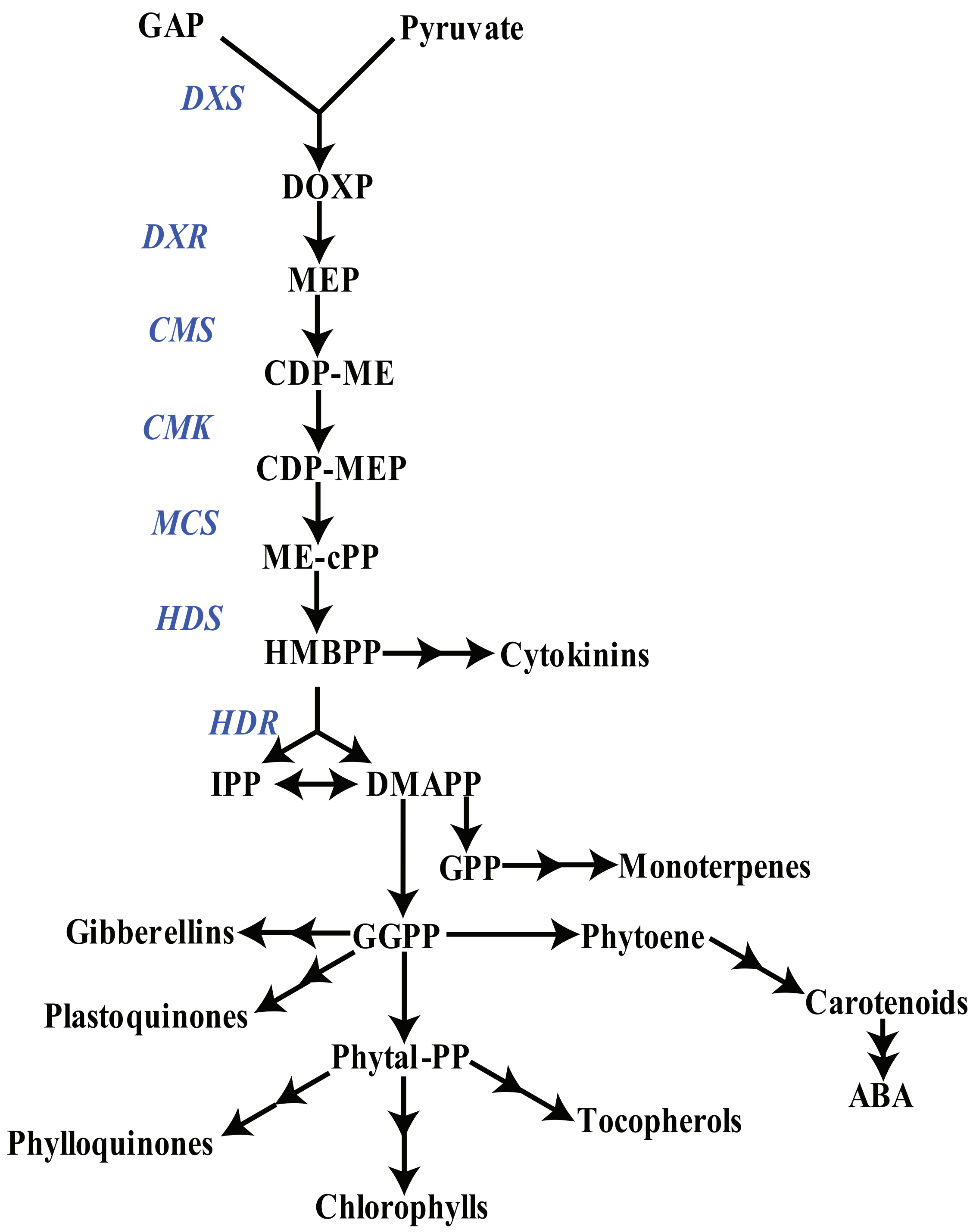

Fig. 1. MEP pathway for the biosynthesis of isoprenoids in plants. ABA, abscisic acid; **CDP-ME, 4-(cytidine-5'-diphospho)-2-C-methyl-D-Erythritol**; **CDP-MEP, 4-Diphosphocytidyl-2C-methyl-D-erythritol 4-phosphate**; DMAPP, dimethylallyl diphosphate; **DXP, 1-deoxy-D-xylulose 5-phosphate**; GAP, glyceraldehyde 3-phosphate; GGPP, geranylgeranyl diphosphate; GPP, geranyl diphosphate; **HBMPP, 4-hydroxy-3-methylbut-2-enyl diphosphate**; IPP, isopentenyl diphosphate; **ME-cPP, 2C-methyl-D-erythritol 2,4-cyclodiphosphate**; **MEP, 2C-methylerythritol 4-phosphate**. Enzymes are indicated in bold italic; 4-(cytidine-5'-diphospho)-2-C-methyl-D-Erythritol kinase **(CMK, EC 2.7.1.148)**; 4-Diphosphocytidyl-2C-methyl-D-erythritol 4-phosphate synthase **(CMS, EC 2.7.7.60)**; 1-deoxy-D-xylulose 5-phosphate reductoisomerase **(EC 1.1.1.267)**; 1-deoxy-D-xylulose 5-phosphate synthase **(DXS, EC 4.1.3.37)**; 4-hydroxy-3-methylbut-2-enyl diphosphate reductase **(HDR, EC 1.17.1.2)** ; 4-Hydroxy-3-methylbut2-en-yl-diphosphate synthase **(HDS, EC, 1.17.4.3)**; 2C-methyl-D-erythritol 2,4-cyclodiphosphate synthase **(MCS, EC 4.6.1.12)**.

(EC 4.1.3.37). DOXP then undergo intra-molecular rearrangement and reduction catalysed by 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR, **EC 1.1.1.267)** to yield methyl erythritol-4-phosphate (MEP) which is regarded as an immediate precursor of plastidic isoprenoids. MEP is consecutively converted into 4-diphosphocytidyl-methylerythritol (CDP-ME), 4-diphosphocytidyl-methylerythritol (CDP-MEP) and methyl-erythritol 2,4-cyclodiphosphate (ME-cPP). These reactions are carried out by CDP-ME synthase (CMS, **EC 2.7.7.60**), CDP-ME kinase (CMK, **EC 2.7.1.148**) and ME-cPP synthase (MCS, **EC 4.6.1.12**). Methyl-erythritol 2,4-cyclodiphosphate (ME-cPP) then converted to hydroxymethylbutenyl 4-diphosphate (HMBPP) by an enzyme hydroxymethylbutenyl 4-diphosphate synthase (HDS, **EC 1.17.4.3**). HMBPP is finally converted into a mixture of IPP and DMAPP by the enzyme HMBPP reductase (HDR, **1.17.1.2**) (Eisenreich *et al*., 2001; 2004).

At present, the genes encoding enzymes of MEP pathway with homology to the *E. coli* MEP pathway enzymes haven been identified from variety of plants including *Arabdopsis thaliana* (http://www.Arabidopsis.org). The present review is aimed to provide the information on these cloned and characterized genes of MEP pathway in plants. Basically, the idea to compile the information on MEP pathway genes came from a very likely article on cloned genes of acetate-MVA pathway in plants by Scolink and Bartley (1996). The information about cloned genes of MEP pathway in one piece would be helpful to home in to isoprenoid biosynthesis. The results presented here were derived through online search and analysis (http://www.ncbi.nlm.nih.gov/; http://www.tigr.org/). In addition, published literatures were also taken in account such as those describe application of ^{13}C-glucose-Nuclear Magnetic Resonance (NMR) spectroscopy for elucidation of MEP pathway in plants. In addition, we took the help of bioinformatics tools to search DXS and HMGR, two key enzymes of their respective pathways to investigate these pathways in plants.

^{13}C-glucose-NMR spectroscopy provides clues for the MEP pathway

The potential of using ^{13}C-glucose-NMR spectroscopy to elucidate metabolic pathways in plants has long been recognized. Early efforts relied on NMR spectra of metabolites which were related to the underlying pathways used to create them (Jeffrey *et al*., 1991). NMR spectra have also been used to elucidate the flux through metabolic pathways (Bacher *et al*., 1998; Kelleher, 2001). The use of *in vivo* ^{13}C-NMR spectroscopy to study the biosynthesis of secondary metabolites in plants has been well documented previously (see Table 2). Useful clues to the origin of the carbon atoms of isoprenoids in bacteria and for the elucidation of the MVA independent route were obtained from labeling experiments using ^{13}C-glucose with *Zymomonas mobilis*, a facultative anaerobic and fermentative bacterium (Sprenger, 1996). The use of NMR spectroscopy in plant secondary metabolism has been hampered mainly because of very low concentration of the secondary metabolites, and the pathway leading to isoprenoid formation are often branched hence the ^{13}C-label of early precursors is diluted into several metabolites at the end. These difficulties in resolving the origin of Isoprenoid units could be overcome by NMR analysis of extracts or isolated compounds. To investigate the biosynthetic origin of isoprenoid building blocks of secondary metabolites, the pathway-independent precursor ^{13}C-glucose, which produces distinctly different labelling patterns of the individual isoprene units for the MEP and MVA pathways is generally employed (Rohmer, 1999). Given that glucose is a general intermediary metabolite, the isotope from the proffered carbohydrate can be diverted to virtually all metabolic compartments and intermediates in plant cells (Eisenreich *et al*., 2004).

The biosynthetic origin of a considerable number of primary and secondary plant terpenoids has been and currently being reinvestigated using ^{13}C-glucose-NMR spectroscopic technique in higher and lower plants (liverworts). Table 1 provides the information on application of ^{13}C-NMR spectroscopy to elucidate the MEP pathway in plants. The data show that a wide variety of monoterpenes, diterpenes and sesquiterpenes (germacrene) are biosynthesized predominantly *via* the MEP pathway. Beside the analysis of these published reports on MEP pathways, our online database search for DXS and HMGR the key regulatory enzyme respectively of MEP and acetate-MVA pathways further provided the clue for the operation of either of these pathways in plants. Table 2 provides information on distribution of DXS and HMGR enzymes in plants. This information was collected online from http://www.ncbi.nlm.nih.gov/.

Cloned genes of MEP pathway

Our knowledge and understanding about the biosynthesis and regulation of isoprenoids in plants has been tremendously increased during the past two decades. As a result, genes encoding enzymes of the MEP pathway have been cloned and characterized from a several plants in the recent time. Though, several genes of the MEP pathway downstream from *ispC* were discovered by a strategy combining biochemical evidence with comparative genomic analysis. Please see a review by Eisenreich *et al*. (2004) for detailed description about the mechanism of action of enzymes of MEP pathway. Here in the Table 3 we provide information exclusive on cloned and characterized genes of the MEP pathway in plants. The information mainly comprises of GeneBank accession number, size and protein or gene name. Table 3 shows that DXS and DXR have been cloned and characterized from a variety of plants while other enzymes of the MEP pathway could only be characterized only from a few plants. So far, HDS is known from only two plants *Nicotiana benthamiana* and *Oryza sativa*. Similarly HDR is also known from only two plants, *Arabidopsis thaliana* and *N. benthamiana*. An overall distribution of MEP genes in plants is presented in Table 4. From Table 4, it is clear that *A. thaliana* and *O. sativa* (Japonica var.) genome has complete set of genes encoding enzymes of MEP pathway along with HMGR of acetate-MVA pathway. *Stevia rebaudiana* genome has shown at least six of the seven genes of MEP pathway, but lacks the HMGR of acetate-MVA pathway. Further analysis of the data has revealed that 19 out of 39 plants searched online have

Table 1. MEP pathway in plants verified on the basis of ^{13}C-glucose-NMR spectroscopy.

Plants	Isoprenoids	References
Catharanthus roseus	Terpenoids Iridoid glucoside secologanin	Arigoni *et al*., 1997; 1999; Contin *et al*., 1998
Chelidonium majus *Populus nigra* *Salix viminalis*	Isoprene	Zeidler *et al*., 1997, 1998
Conocephalum conicum	Isoprenoids	Thiel *et al*., 2002
Dacus carota *Hordeum vulgare* *Lemna gibba*	L-carotene, lutein, prenyl chains of chlorophylls and plastoquinone-9	Lichtenthaler *et al*., 1997
Eucalyptus globules	Cineol	Rieder *et al*., 2000
Fossombronia alaskana	Hopane triterpene and three diterpenes	Hertewich *et al*., 2001
Hordeum vulgare	sesquiterpenoid cyclohexane derivatives	Maier *et al*., 1998
Liriodendron tulipifera	Terpenes	Sagner *et al*., 1998
Marrubium vulgare	Labdane diterpenoid marrubin	Knoss *et al*., 1997
Matricaria recutita	Isoprene units of chamomile sesquiterpenes	Adam and Zapp, 1998
Mentha citrate	Linalyl Acetate monoterpene	Fowler *et al*., 1999
Mentha pulegium	Monoterpenes	Eisenreich *et al*., 1997
Narcissus pseudonarcissus	*b*-carotene	Fellermeier *et al*., 1999
Pelargonium graveolens *Thymus vulgaris*	Monoterpenes	Eisenreich *et al*., 1997
Persea Americana	Abscisic acid; Carotenoids and abscisic	Hirai *et al*., 2000; Milborrow *et al*., 1998
Rauwolfia serpentine	Monoterpene loganin	Eichinger *et al*., 1996
Taxus chinensis	Taxol (diterpene)	Eisenreich *et al*., 1996
Trichcolea tometella	Trichcolein and deoxytometellin (Hemi- and mono- terpene moieties and diterpene phytol)	Barlowa *et al*., 2003
Vitis Vinifera	Linalool and geraniol	Klink *et al*., 2005
Lepidolaena hodgsoniae	Sesquiterpene hodgsonox	Luan *et al*., 2002
Anisotome layallii	Anisotomenes (bicyclic irregular diterpenes)	Barlowa *et al*., 2003
Piper aduncum	Isoprene Units in Chromenes	Leite *et al*., 2007
Solidago Canadensis	Germacrene D (sesquiterpenes)	Steliopoulos *et al*., 2002

genes of both MEP and acetate-MVA pathway in their genome, while the others 20 plants had exclusively genes of MEP pathway.

Conclusion

Many pathogenic microorganisms including *Mycobacterium tuberculosis* and *Plasmodium falciparum* also operate MEP pathway for the biosynthesis of isoprenoids. In fact, isoprenoids plays crucial role in the survival of *P. falciparum* in host cells. Knowledge of the MEP pathway in such pathogenic microorganism is currently being exploited for the development of structure-based anti-microbial drugs by targeting the enzymes of MEP pathway. Therefore, details concerning the genes, enzymes and intermediates of the MEP pathway have become essential in achieving these goals. Currently, fosmidomycin an inhibitor of DOXP reductoisomerase (DXR) of MEP pathway has been successfully tested to hang-up isoprenoid biosynthesis in *P. falciparum*. Similar strategies could be employed for the development of novel herbicides (Lichtenthaler *et al*., 2000). This aspect of the isoprenoids researches have a direct impact on human health, hence created much interest and awareness among the researchers in the recent years to look for new structure based drugs against more pathogenic microorganisms and weeds relying on MEP pathway. Our, knowledge and understanding about the plant secondary metabolite biosynthesis and regulation has greatly accelerated these efforts. Most certainly, comparative genomics and in combination of bioinformatics has been an aid.

Acknowledgements

Authors are grateful to the Chancellor, VIT University for providing the necessary support and Professor Lazar Mathew and Professor Braj Nandan Prasad, School of Biotechnology, Chemical and Biomedical Engineering, VIT University for their constant encouragement and valuable suggestions. Financial support from the Department of Sciences and Technology (DST) and Council of Scientific and Industrial Research (CSIR), New Delhi, Government of India is duly acknowledged.

Table 2. Results of online search for DXS and HMGR. DXS is assigned to MEP whereas HMGR to acetate-MVA pathway.

	MEP Pathway DOXP Synthase (DXS)		Acetate-Mevalonate Pathway HMG-CoA Reductase (HMGR)	
Plants	Accession No.	Size	Accession No.	Size
Arabidopsis thaliana	BAB02345	604	AAA67317	562
Antirrhinum majus	AAW28999	733		
Artemisia annua	AAD56390	713	AAD47596	567
Andrographis paniculata	AAP14353	691	AAP14352	556
Camptotheca acuminate			AAB69726	575
Capsicum annuum	CAA75778	719	AAD28179	604
Catharanthus roseus	CAA09804	716	AAT52222	601
Cistus incanus subsp. creticus			ABL10110	388
Chrysanthemum x morifolium	BAE79547	669		
Elaeis guineensis	AAS99588	707		
Ginkgo biloba	AAS89341	717	AAU89123	571
Hevea brasiliensis	AAS94123	720	CAA38467	575
Lycopersicon esculentum	AAD38941	719	AAB62581	601
Lycopersicon hirsutum	AAT97962	714		
Mentha x piperita	AAC33513	724		
Medicago truncatula	ABP03805	711	ABE88827	583
	ABP03804	710		
	ABO82094	717		
Morinda citrifolia	AAL32062	722		
Narcissus pseudonarcissus	CAC08458	709		
Nicotiana tabacum			AAB87727	604
			AAO85554	604
Oryza sativa (Japonica)	NP_001055524	720	BAD10066	561
Oryza sativa (Indiaca)	EAY98024	710	CAA92821	576
	AAB88295	594		
Pueraria montana var. lobata	AAQ84169	717		
Picrorhiza kurrooa			ABC74565	561
Salvia miltiorrhiza			ABB45812	174
			AAU87798	267
Stevia rebaudiana	CAD22155	715		
Tagetes erecta	AAG10432	725	AAC15475	574
Taxus cuspidate				
Taxus x media	AAS89342	742	AAQ82685	595
Zea mays	ABP88134	719	CAA70440	579
	ABP88135	705		
	AAX49359	481		
	AAX49358	424		
Vitis Vinifera	CAN71054	1638	CAN72217	575

DOXP: 1-deoxy-D-xylulose 5-phosphate; HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A.

Table 3. Cloned and characterized enzymes of the MEP pathway in plants.

Enzyme	Plant	Accession numbers	Size	Protein / Gene	Reference
1-deoxy-D-xylulose 5-phosphate synthase (DXS, EC 4.1.3.37)	*Arabidopsis thaliana*	NP_001078570	565	DXPS3	Sato *et al.*, 2000
		NP_196699	700	DXPS3	
		NP_850620	629	DXPS1	
		BAB02345	604	DXS	
	Antirrhinum majus	AAW28999	733	DXPS	Dudareva *et al.*, 2005
	Capsicum annuum	CAA75778.1	719	dxs put.	Bouvier *et al.*, 1996
	Catharanthus roseus	CAA09804	716	DXS	Chahed *et al.*, 1997
	Chrysanthemum x morifolium	BAE79547	669	DXS	Kishimoto *et al.*, 2006
	Croton stellatopilosus	BAF75640	720	dxs	Wungsintaweekul *et al.*, 2008
	Elaeis guineensis	AAS99588	707	dxs	Khemvong *et al.*, 2005
	Ginkgo biloba	AAS89341	711		Gong *et al.*, 2006
	Hevea brasiliensis	AAS94123	720	DXS	Seetang-Nun *et al.*, 2008a
		ABF18929	711	DXS2	
	Lycopersicon esculentum	AAD38941	719	dxs	Lois *et al.*, 2000
	Morinda citrifolia	AAL32062	722	DXS	Han *et al.*, 2003
	Oryza sativa (Japonica)	NP_001055524	720	dxs	Ohyanagi *et al.*, 2006
	Oryza sativa (Indiaca)	AAB88295	594	CLA1	Campos *et al.*, 1997
		TC263109		DXS1	Kim *et al.*, 2005
		TC262788		DXS2	
		TC276717		DXS3	
	Picea abies	ABS50520	746	DXS2B	Phillips *et al.*, 2007
		ABS50519	740	DXS2A	
		ABS50518	717	DXS1	
	Stevia rebaudiana	CAD22155	715	dxs	Totte *et al.*, 2003
	Tagetes erecta	AAG10432	725	dxs	Moehs *et al.*, 2001
1-deoxy-D-xylulose 5-phosphate reductase (DXR, EC 1.1.1.267)	*Arabidopsis thaliana*	CAB43344	406	dxr	Schwender *et al.*, 1999
	Antirrhinum majus	AAW28998	471	dxr	Dudareva *et al.*, 2005
	Camptotheca acuminate	ABC86579	472	Dxr	Yao *et al.*, 2008
	Catharanthus roseus	AAF65154	474	dxr	Veau *et al.*, 2000
	Chrysanthemum x morifolium	BAE79548	487	DXR	Kishimoto *et al.*, 2006
	Ginkgo biloba	AAR95700	477	Dxr	Gong *et al.*, 2005
	Hevea brasiliensis	AAS94121	471	DXR	Seetang-Nun *et al.*, 2008b
	Hordeum vulgare	CAE47438	484	dxr	Hans *et al.*, 2005
	Lycopersicon esculentum	AAK96063	475	DXR	Rodriguez-Concepcion *et al.*, 2001
	Mentha x piperita	AAD24768	470	DXR	Lange and Croteau, 1999
	Oryza sativa (Japonica)	NP_001041780	473	dxr	Ohyanagi *et al.*, 2006
	Oryza sativa (Indiaca)	EAY72208	473	dxr	Yu *et al.*, 2005
	Plectranthus barbatus	AAR99081	469	dxr	Engprasert *et al.*, 2005
	Pueraria montana var. lobata	AAQ84168	465	dxr	Sharkey *et al.*, 2005
	Rauvolfia verticillata	AAY87151	474	DXR	Wu *et al.*, (in Press)
	Salvia miltiorrhiza	ABJ80680	474	DXR	Liao *et al.*, 2007
	Stevia rebaudiana	CAD22156	473	dxr	Totte *et al.*, 2003
	Taxus cuspidate	AAT47184	477	dxr	Jennewein *et al.*, 2004
	Stevia rebaudiana	CAD22156	473	dxr	Totte *et al.*, 2003
	Taxus cuspidate	AAT47184	477	dxr	Jennewein *et al.*, 2004

Table 3. Cloned

Enzyme	Plant	Accession numbers	Size	Protein / Gene	Reference
4-Diphosphocytidyl-2C-methyl-D-erythritol 4-phosphate synthase (CMS, EC 2.7.7.60)	*Arabidopsis thaliana*	NP_565286	302	ISPD	Seki *et al.*, 2002
		BAC42737	302	ispD	
	Ginkgo biloba	AAZ80386	327	MECT	Kim *et al.*, 2005
	Oryza sativa (Japonica)	BAD82130	297	ispD put.	Sasaki and Matsumoto, 2002; Yu *et al.*, 2005
	Oryza sativa (Indiaca)	EAY76759	408	ispD pat.	
4-(cytidine-5'-diphospho)-2-C-methyl-D-Erythritol kinase (CMK, EC 2.7.1.148)	*Arabidopsis thaliana*	O81014	383	ISPE	Lin and Kaul, 1999
	Lycopersicon esculentum	AAF87717	401	ispE	Lange and Croteau, 1999
	Mentha x piperita	P56848	405	ISPE	Rohdich *et al.*, 2000
	Oryza sativa (Japonica)	NP_001044544	401	ispE	Ohyanagi *et al.*, 2006
2C-methyl-D-erythritol 2,4-cyclodiphosphate synthase (MCS, EC 4.6.1.12)	*Arabidopsis thaliana*	AAM62786	231	MECDP_S	Gao *et al.*, 2006
	Ginkgo biloba.	AAY40863	239	Mecps	Alexandrov *et al.*, 2006
	Oryza sativa (Japonica)	EAZ24186	222	MECDP_S	Yu *et al.*, 2005
	Oryza sativa (Indica)	EAY87077	222	MECDP_S	Yu *et al.*, 2005
	Taxus x media	ABB88956	247	mecs	Jin *et al.*, 2006
4-Hydroxy-3-methylbut2-en-yl-diphosphate synthase (HDS, EC, 1.17.4.3)	*Nicotiana benthamiana*	AAS75817	268	gcpE/ispG	Page *et al.*, 2003
	Oryza sativa (Japonica)	AAO72576	608	gcpE	Cooper *et al.*, 2003
1-Hydroxy-2-methyl-butenyl 4-diphosphate reductase (HDR, EC 1.17.1.2) Or, 4-hydroxy-3-methylbut-2-enyl diphosphate reductase	*Arabidopsis thaliana*	AAW82381	468	HDR/ISPH	Guevara-Garcia *et al.*, 2005
	Nicotiana benthamiana	AAS75818	166	ispH LytB	Page *et al.*, 2003

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Table 4: Overall distribution of MEP pathway genes in plants.

	MEP pathway genes							
Plants	*dxs*	*yaeM/dxr*	*ygbP/mect/ispD*	*ychB/cmek/ispE*	*ygbB/mecs*	*gcpE/ispG*	*hdr/ ispH*	*Hmgr*
Arabidopsis thaliana	+	+	+	+	+	+	+	+
Andrographis paniculata	+	−	−	−	−	−	−	+
Antirrhinum majus	+	+	−	−	−	−	−	−
Artemisia annua	+	+	−	−	−	−	−	+
Catharanthus roseus	+	+	−	−	+	−	−	+
Camptotheca acuminate		+						+
Cistus incanus subsp. creticus		+						+
Chrysanthemum x morifolium	+	+	−	−	−	−	−	−
Citrus jambhiri						+		?
Croton stellatopilosus	+	+	−	−	−	−	−	−
Elaeis guineensis	+	+	−	−	−	−	−	−
Forsythia x intermedia	+	+	−	+	−	−	+	−
Ginkgo biloba	+	+	+	+	−	−	+	+
Hevea brasiliensis	+	+	−		−	+	−	+
Hordeum vulgare		+						−
Linum usitatissimum		+						−
Lycopersicon esculentum	+	+	−	+	+	−	−	+
Lycopersicon hirsutum	+	−	−	+	−	−	−	−
Mentha x piperita	+	+	−	+	−	−	−	−
Medicago truncatula	+	−	−	−	−	−	−	+
Mesostigma viride				+			+	?
Morinda citrifolia	+	−	−	−	−	−	−	−
Narcissus pseudonarcissus	+	−	−	−	−	−	−	−
Nicotiana benthamiana				+	+		+	−
Nicotiana tabacum		+						+
Oryza sativa (Japonica)	+	+	+	+	+	+	+	+
Oryza sativa (Indiaca)	+	+	+	−	−	+	−	+
Picrorhiza kurrooa		+		+				+
Plectranthus barbatus		+						−
Pueraria montana var. lobata	+	+	−	−	−	−	−	−
Rauvolfia verticillata		+		+				−
Salvia miltiorrhiza		+	+	+				+
Stevia rebaudiana	+	+	+	+	+	+	−	−
Tagetes erecta	+	+	−	−	−	−	−	+
Taxus chinensis		+						−
Taxus cuspidate		+						−
Taxus x media	+	+	−	−	−	+	−	+
Vitis Vinifera			+					+
Zea mays	+	+	−	−	+	−	−	+

dxs: 1-deoxy-D-xylulose 5-phosphate synthase; ***dxr*:** 1-deoxy-D-xylulose 5-phosphate reductase; ***ispD*:** 4-diphosphocytidyl2*C*-methyl-D-erythritol synthase; ***ispE*:** 4-diphosphocytidyl 2*C*-methyl-D-erythritol kinase; **mecs**; 2*C*-methyl-D-erythritol 2,4-cyclodiphosphatesynthase; ***ispG*:** 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate synthase; ***ispH*:** 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate reductase; ***hmgr*:** 3-hydroxy-3-methylglutaryl-CoA reductase.

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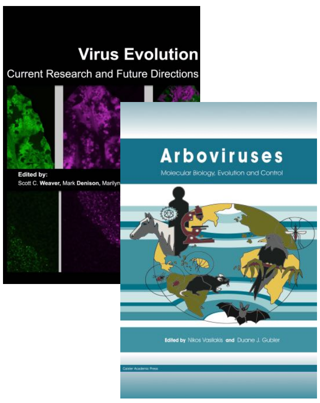

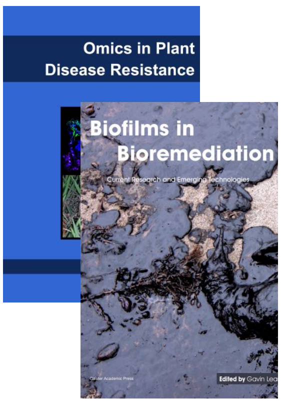

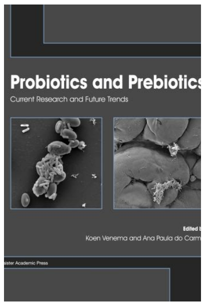

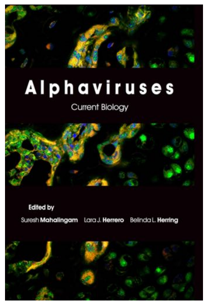

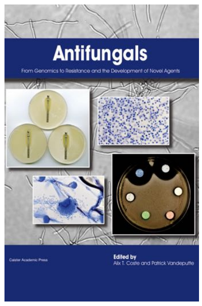

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