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Expression of secondary metabolites in plants and their useful perspective in animal health

Ali Parsaeimehr, Elmira Sargsyan, and Anush Vardanyan

G. S. Davtyan Institute of Hydroponics Problems, National Academy of Sciences Republic of Armenia, Yerevan, 375082, Armenia. Corresponding author: A. Parsaeimehr, Ali.Parsaeimehr@gmail.com

Abstract. In today's world the usage of useful secondary metabolites derived from plants metabolisms pathways plays important roles in pharmaceutical productions and applications. These metabolites such as Apigenin an anti-infection, anti-viral, anti-carcinogenic derived from *Anthemis nobilis* plants or Berberine an anti- microorganism, Anti diabetic, anti-inflammatory activity, anti-cancer, LDL cholesterol reducer derived from *Berberis aquifolium*, are constantly used in pharmaceutics. This paper tries to present some information about some of these metabolites and the usage of them.
Key Words: Plant secondary metabolites, Alkaloids, phenols, Terpenes.

Аннотация. В современном мире использование вторичных метаболитов, как продукт метаболизма растений, играет важную роль в фармацевтическом производстве. В данной статье представлена информация о некоторых вторичных метаболитах растений и их применение в медицине. Такие ценные метаболиты, как апигенин получаемый из *Anthemis nobilis, Thymus serpyllum, Achillea millefolium* и др. и берберин - из *Berberis aquifolium,* обладают антимикробной, антивирусной, антиканцерогенной, антивоспалительной активностями. Берберин является антидиабетическим средством и LDL холестерин редуктором.
Ключевые Слова: вторичные метаболиты растений, алкалоиды, фенолы, терпены

Introduction. Plants have existed for millions of years and numerous animals and insects have coevolved with them. Undoubtedly one of the brilliant aspect of their surviving in the nature is about the production of some metabolites known as secondary metabolites (allelochemicals) by certain pathways that are known to be produce under harsh conditions. Considerably, herbivorous animals and insects use the plants as a source for their existence while the plants staidly express these metabolites as a defensive mechanism, or even carnivorous plants have the ability to trap insects in the specialized organs, obtaining additional nitrogen and phosphorus in nutrient-poor environments (Stotz et al 1999). The host-plant resistance (HPR) mechanism of plants starts by certain pathways that initiated from gene expression which consequently leads to express compounds such as: Tannins, Alkaloids, Phenols, Resins, etc.

Plant secondary metabolites are categorized in three main branches based on their biosynthesis pathways: Phenolic compounds, Terpenes and Nitrogen-containing compounds. It is proven that Terpenes synthesise via mevalonic pathway from pre-processor of Acetyl CoA, while Phenolic compounds are aromatic substances formed via Shikimic acid pathway or mevalonic pathway and considerably the Nitrogen containing secondary metabolites such as Alkaloids synthesise primarily from Aliphatic amino acids derived from Tricarboxilic acid cycle pathway or Aromatic acids derived from Shikimic acid pathway. These introduced classes of metabolites have been widely used in pharmaceuticals. This manuscript tries to present information about the expression of some useful secondary metabolites and their fascinated usage in pharmaceutics.

Phenolic compounds. Plants biosynthesis of the Phenolic compounds regards to the growth, reproduction, pigmentation, resistance to pathogens, influences of heavy metal-salts or in a general form under influences of biotic and a-biotic stresses. These fabulous compounds are consisting hydroxyl groups which attached to an aromatic hydrocarbon group and most of them show estrogenic activities. Different classes of Phenols have been classified from their skeleton structure from simple Tannins to more complex ones like polymeric Flavonoids (Halbwirth 2010; Uyama 2007). Even though it was reported that, the Phenols are acting as constitutive defenders against pathogens and their main activity is to serve as an inhibitor to block the pathogens access but too many aspects of their expression still remain ambiguous.

Considerably, among Phenolic contents Coumarin ($C_9H_6O_2$) with the base of benzopyrone and derived from Shikimic acid pathway is found in vascular plants such as: *Galium odoratum, Cinnamomum aromaticum*, *Hierochloe odorata* and *Melilotus* species. It is proven that, the biosynthesis of Coumarin occurs by hydroxylation, glycolysis and cyclization of Cinnamic Acid. Correlatively, compounds such as Furano-coumarins, Ligin, Flavonoids, Isoflavonoids, Tanins are covered as Phenols. By the reports beside biotic stresses such as pathogens, insects or herbivores, abiotic stresses like UV or Ozone can also act as an elicitor to induce Phenolic compounds, for example the phenolics increased significantly in blueberries under UV treatments (*Vaccinium corymbosum*) or even it has been reported that UV radiation causes the flavonoids gene pathway expression that it consequently leads to accumulate the phenolics in the leaves of *Betula pendula* or even the elevated Ozone increased the concentrations of phenolics and antioxidant in red clover (*Trifolium pratense*) leaves (Eichholz et al 2010; Morales et al 2010; Saviranta et al 2010). Reports have demonstrated the significance inhibitory influences of Phenolic compounds on pathogens and insects, while the in vitro growth of *Xylella fastidiosa,* a pathogenic bacterium that causes diseases in many crop species was limited where Phenolic compounds had been expressed in the samples or the coffee genotypes which expressed the highest levels of Phenolics were showed highest resistance to the leaf miner *Leucoptera coffeella,* a serious coffee pest (Magalhães et al 2010).

Researchers have stated that, the Phenolic contents were changed under different circumstances; correspondingly Hughes et al (2010) claimed that Phenolic content in *Veronica spp* was altered in the species while it was consistently higher in leaf margins compared with leaf interiors, meanwhile they have also claimed that, the mean Phenolic content was inversely correlated with the mean length of continuous insects bites in the plant.

It was reported that, fungal induction led to accumulation of Lignin, Phenolic glycosides and Stilbenes in the phloem of Austrian pine tree (Wallis et al 2008). Regard to the plant and fungi interactions there are sufficient evidences that different Phenolic compounds such as: Benzaldehyde, Ethyl benzoate, 3,4-Dihydroxybenzaldeyde, Catechol, Protocatechuic acid, 2,5-Dimethoxybenoic acid, Salicylic acid, Vanillic acid, 4-Hydroxybenzoic acid, Chlorogenic acid, *p*-Coumaric acid, Cyanidin, 3-and7-Hydroxyflavone, Dihydroquercetin, Naringenin, Flavone, Oleuropin, Nobiletin, Biochanin and Genistein are over synthesized and expressed by plants under fungus attacks (Lattanzio et al 2006).

The correlation between Phenols and Antioxidants is not novel and there are sufficient existent information about it, undoubtedly the conception of antioxidant action of phenols is related to their hydroxyl and carboxyl groups and their particular ability to bind to Copper, Iron and in general their tendency to chelate metals. In this regards Antioxidant and total Phenolic compounds of *Orthosiphon stamineus* were investigated by using the assays of Folin Ciocalteu and DPPH tests and the results showed that the phenolics and antioxidants are highly correlated together (Abdelwahab et al 2011). Meanwhile, the antioxidant values were highly correlated with total Phenol content in Berry fruits, whereas a smaller linear correlation had existed between antioxidant capacity and total Anthocyanin content (Wang 2011).

Flavonoids are commonly found in most plants, and they are the pharmacologically active constituents in many herbal plant medicines. It is also reported that, the consumption of certain plant materials may reduce the risk of chronic diseases related to oxidative stress on account of their antioxidant activity and promote general health benefits.

Table 1

List of some important phenols and their mechanism of action

Phytochemical compound	*Chemical formula*	*Plant*	*Mechanism of action*
Apigenin	4',5,7-trihydroxyflavone	*Chamaemelum nobile, Anthemis nobilis, Matricaria recutita, Achillea millefolium, Apium graveolens, Artemisia dracunculus, Camellia sinensis, Chamaemelum nobile, Coriandrum sativum, Gingko biloba, Glycyrrhiza glabra, Marrubium vulgare*	Anti infection, antiviral, anticarcinogenic activity (Duke & Beckstrom-Sternberg 2000; Lepley et al 1996; Nielsen et al 1999; Breinholt et al 1999; Jeong et al 1999).
Diosmin	3',5,7-Trihydroxy-4'-methoxyflavone 7-rutinoside	*Citrus aurantium, Hyssopus officinalis, Vicia ervilia*	It was used to treat chronic venous insufficiency, lymphedema, and varicose veins and also as an effective antioxidant and anti-inflammatory agent (Sandhar et al 2011; Jiménez Cossío et al 1991; Ivashev et al 1995).
Luteolin	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromenone	*Halenia corniculata, Pyrola rotundifolia, Gentiana tenella, Reseda luteola, Achillea millefolium, Thymus vulgaris, Limonium sinuatum, Vitex rotundifolia, Erigeron canadensis, Sophora angustifolia, Satureja obovata, Lonicera japonica*	Antioxidant, cardiovascular activity, anticarcinogenic, anti-inflammatory activity, antidiabetic activity, antiallergy activity and anti microorganism activity (Odontuya et al 2005; Ko et al 2005; Gutiérrez-Venegas et al 2006; Lee et al 2006).
Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4 H-chromen-4-one.	*Podophyllum peltatum, Cephalotaxus harringtonia, Dysoxylum malabaricum, Maytenus serrata, Thapsia garganica*	Antihypertensive, antioxidant, antimutagenic, anticoagulant and anticarcinogenic (Cragg & Newman 2005; Larson et al 2010; Davis et al 2009).
Kaempferol	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one	*Foeniculum vulgare, Kaempferia pulchra, Zingiber zerumbet, Alpinia conchiger, Pedilanthus tithymaloide, Jatropha podagrica, Tibouchina semidecandra, Rhodomyrtus tomentosa, Cymbopogon nardu, Polycias scutellaria*	Strong antioxidant, anticarcinogenic, anti-inflammatory activity and anti microorganism activity (Chew et al 2009; Hämäläinen et al 2007).
Galangin	3,5,7-trihydroxy-2-phenylchromen-4-one	*Alpinia officinarum, Helichrysum aureonitens, Rubia cordifolia, Glycyrrhiza glabra*	Antioxidant, anticarcinogenic, anti-inflammatory activity, anti microorganism activity (Kaur et al 2010).
Fisetin	2-(3,4-hihydroxyphenyl)-3,7-dihydroxychromen-4-one	*Fragaria spp, Rhus verniciflua*	Antioxidant, anticarcinogenic, anti-inflammatory activity, and anti microorganism (Lee et al 2002; Gideon 2003).
Myricetin	3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4-chromenone	*Cephalotaxus harringtonia, Bleekeria vitensis, Dysoxylum binectariferum, Euphorbia semiperfoliata*	Antioxidant, anticarcinogenic, anti microorganism, antidiabetic (Laughton et al 1989; Ong 2000).

Nitrogen compounds. Secondary metabolites derived from Nitrogen are classified as: Alkaloids, non-protein Amino acids, Amines, Alcamides, Cyanogenic glycosides and Glucosinolates (Paiva et al 2010). Perhaps the response to the question, why these compounds and especially Alkaloids are active substances, is relied on the molecular skeleton of the Alkaloids. Considerably, Alkaloids such as Pyrrolidine, Tropane, Pyrrolizidine, Piperidine, Quinolizidine, Pyridine derivatives, Isoquinoline derivatives, Colchicine etc. are discovered in different plant families and most of them are famous because of their pharmaceutical potential.

Among Alkaloids, Coniine derived from *Conium maculatum* is extremely toxic and affects the nerve system or Sanguinarine, an alkaloid derived from *Sanguinaria canadensis* has a toxic action on the Na^{+}-K^{+}-ATPase trans-membrane protein. Nicotine, an essential Alkaloid from *Nicotiana tabacum* existed in a number of other plants of the families of Lycopodiaceae, Crassulaceae, Leguminosae, Chenopodiaceae and Compositae (Lee et al 1993). It was reported that, Nicotine had inhibitions on the tobacco hornworm, *Manduca sexta* and cigarette beetle, *Lassioderma serricorne*. It seems that, the widely usage of Nicotine as one of the first insecticides used to control pests in agriculture lays behind Schmeltz (1971) explanation about this fabulous Alkaloid that, the pyridine alkaloid Nicotine is one of the best-studied putative plant resistance traits because it can interact with the Acetylcholine receptors in the nervous systems of animals and therefore Nicotine is extremely toxic to most herbivores.

Among the alkaloids Caffeine, a purine alkaloid, plays as a chemical defense compound against pathogens and also herbivores and even as it is recognized as an allelopathic compound among plants (Ashihara et al 2008; Baumann & Gabriel 1984). There are also fabulous reports about the usage of Alkaloids in pharmaceuticals as an instance Rauwolscine, an alkaloid derived from *Rauwolfia canescens* is reported as a Central nervous stimulator or Coralyne as DNA-binding agent and anti-cancer, antioxidant, anti-inflammatory agent (Table 2).

Alkaloids constitute enormous numbers of phytochemicals of toxicological, pharmacological, nutritional and cosmetic interest, and of ecological importance for plants. Tropane alkaloids include Cocaine and Atropine, Nicotine is a Pyridine alkaloid, Noradrenaline (or Norepinephrine), and Adrenaline (Epinephrine), Papaverine, Curarines and Morphine arise from Tyrosine (Iriti & Faoro 2009). Melatonin and Serotonin are Indolamines, Vindoline, Catharantine are Indole alkaloids, Quinine and Capthotecin are Quinoline alkaloids and Lysergic acid Diethylamide (LSD) is an ergot alkaloid, all these arising from Tryptophan (Figure 1). Importantly, purine alkaloids include Theophylline, Theobromine and Caffeine, and they can be found in tea, cacao and coffee, respectively (Table 2).

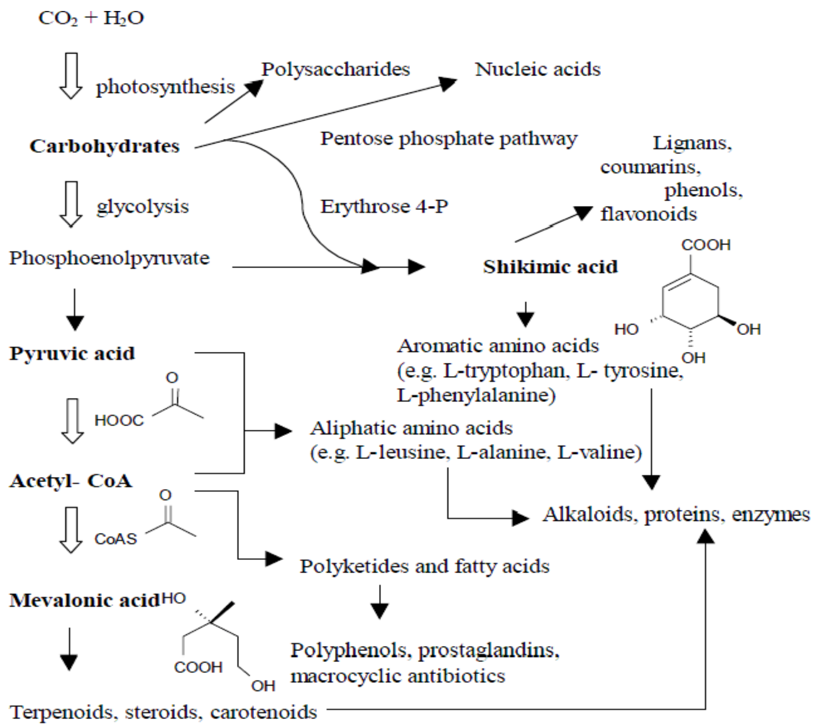

Figure 1. The common biosynthetic pathways of secondary metabolites via Acetyl-CoA, Shikimic acid, Mevalonic acid (Tolonen 2003).

Table 2

Some important alkaloids and their mechanism of action

Phytochemical compound	*Plant source*	*Mechanism of action in mammals*
Ephedrine, Pseudo-Ephedrine, Norpseudoephedrine (Cathine), Norephedrine, Methylephedrine, Methylpseudoephedrine	*Ephedra sinica*	Central nervous and cardiac system; stimulation of ɑ and ß receptors; semi-adrenaline, anti-hypersensitivity, anti-inflammatory, anti-allergic, anti-asthma activity (Zgourides et al 1989; Hoffman et al 1996; Furu et al 2007; Parsaeimehr et al 2010).
Caffeine	*Coffea arabica*, *Camellia sinensis*, *Theobroma cacao*	Increased arousal and decreased sleep, increase the cautiousness by influence on central nervous system (CNS), and inhibitory actions in synthesis of adenosine A1 and A2 receptors (Lane et al 1990, 2002)
Physostigmine (Eserine)	*Physostigma venenosum*	Inhibitors of Neurotransmitter - Degrading enzymes, acetylcholinesterase inhibitor, actions on the neuromuscular junction (Alderdice 1982).
Berberine, Coptisine, Norlaudanosoline	*Bocconia frutescens, Papaver rhoeas, Berberis aquifolium*, *Hydrastis canadensis*, *Phellodendron amurense*, *Coptis chinensis*, *Eschscholzia californica*	Anti microorganism, anti diabetic, anti-inflammatory activity, anti cancer, LDL cholesterol reducer, antidepressant, and positive inhibitory effects on HIV (Lin et al 2004; O'Hara et al 1998).
Coralyne, Chaconine, Demissine, Solarmargine, Solanine, Solanidine	*Solanum lycopersicum*, *S. tuberosum, S. melongena*	DNA-binding agent and anti-cancer, antioxidant, anti-inflammatory agent, and anti microorganism (Lee et al 1993; Bhadra et al 2008).
Harmaline, Harmine	*Banisteriopsis caapi, Peganum harmala*	Central nervous stimulator, anti-cancer, antibacterial (Zaker et al 2007).
Rauwolscine, Corynanthine	*Rauwolfia canescens*	Central nervous stimulator (Mammoto et al 1996).

Terpenes. Terpenes are lipid-soluble compounds (Table 3) and their structure includes 1 or more 5-carbon Isoprene unites, which are ubiquitously synthesized by all organisms through 2 potential pathways, the Mevalonate and, more recently identified, Deoxy-d-xylulose pathways (Rohmer 1999). Terpenoids are classified according to the number of Isoprene units they contain; Isoprene, which itself is synthesized and released by plants, comprises 1 unit and is classified as a Hemiterpene; Monoterpenes incorporate 2 isoprene units, Sesquiterpenes incorporate 3 units, Diterpenes comprise 4 units, Sesterpenes include 5 units, Triterpenes incorporate 6 units, and Tetraterpenes 8 units and considerably, Terpenes and Terpenoids are the base constituents of many types of plant's essential oils. It is proven that, the Terpenes have great biological activities such as: anti-cancers, anti microorganisms and anti inflammatory (Liu et al 2000). Terpenes in plants are synthesised by Mevalonic acid pathway and they play some functional roles in primary metabolism and considerably, the hormones such as Gibberellins and Abscisic acid and pigments such as Phytol and Carotenoids are a part of Triterpenoids.

Meanwhile, Resins in plants are Monoterpenes or Pyrethum and Azadirachtin from *Chrysanthemum* spp and Meliaceae family as natural insecticides are Terpenes. Considerably, Menthol as a Terpen is reported to have anti-herbivores influences and its smell warns that the plant contains toxic compounds.

Table 3

Some important Terpenes and their mechanism of action

Phytochemical compound	*Plant source*	*Mechanism of action in mammals*
Cardenolides	*Digitalis purpurea, Calotropis procera*, *Asclepias* spp	Influence Na^+/K^+ ATP-ase of heart muscle and it used to treat heart disease (Hagimori et al 1982; Seiber et al 1982).
Saponins	Family of Caryophyllaceae, Sapindaceae, Hippocastanaceae, and *Gynostemma sp.*	Anti-cancer, anti-inflammatory, anti-fungal, anti-viral or even anti HIV-1 (Yang et al 1999; Liu et al 2000).
Limonene	Family of Rutaceae	Dietary anticarcinogen (Zhao & Singh 1998).
Artemisinin	*Artemisia annua*	Anti-malarial, used anti-cancer (Nakase et al 2008; Dell'Eva et al 2004).
Taxol	*Taxus brevifolia*	Antileukemic, antitumor (Pandi et al 2011).

The usage of biotechnology in production of secondary metabolites. Many biotechnological strategies have been hypothesized and used to enhance the production of secondary metabolites in plants such as: high yielding cell line screening, optimization of the media, biosynthesis pathways engineering, usage of the elicitors, large scale cultivation in bioreactor system, hairy root culture, plant cell immobilization, biotransformation. Several strategies have been followed to improve yields of secondary metabolites in plant cell cultures. First of all, as common approaches, the screening and selection of high producing cell lines and the optimization of growth and a production medium can be mentioned, for example in the cases of Shikonin and Berberine with success, in many others with limited success. In the past years new approaches have been developed such as: the culturing of differentiated cells (i.e., shoots, roots and hairy roots), induction by elicitors and metabolic engineering. Undoubtedly, in most cases the cultures of differentiated cells have been able to get productions of the desired compounds in levels comparable to the mother plant; however the culture of such differentiated tissues on a large-scale in bioreactors is a major constraint but for studies of the secondary metabolites biosynthesis such systems are very useful. The second approach is mentioned as the use of elicitors, this technique has been successfully reported in several cases. However, it remains limited to a certain type of compound for each plant, compounds which most likely act as Phytoalexins in these plants. Plant cell cultures provide an excellent system to study biosynthesis of secondary metabolites for the large scale production of these compounds, but unfortunately in most cases production is too low for commercialization, therefore advances in biotechnology particularly in plant cell cultures methods, should provide new means for the commercial processing of even rare plants and the chemicals they provide. These new technologies will extend and enhance the usefulness of plants as renewable resources of valuable chemicals. There has been considerable interest in plant cell cultures as a potential alternative to traditional agriculture for the industrial production of secondary metabolites (Dicosmo & Misawa 1995). Plant cell culture technologies were introduced at the end of 1960s as a possible tool for both studying and producing plant secondary metabolites. Different strategies using cell cultures systems have been extensively studied with the objective of improving the production of bioactive secondary metabolites and cell culture systems could be used for the large scale culturing of plant cells from which secondary metabolites can be extracted. The advantage of this method is that it can provide a continuous, reliable source of natural products.

Conclusion. As it were reported, there are brilliant and significant usages of derived secondary metabolites in pharmaceutical industries which these approaches has annually led to billions of dollars profits, and undoubtedly the combination of fascinated technologies such as genetic engineering, tissue culture or the engineering of biosynthesis pathways will make these significant more valuable.

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Authors:
Ali Parsaeimehr, G. S. Davtyan Institute of Hydroponics Problems, National Academy of Sciences Republic of Armenia, Yerevan, 375082, e-mail: Ali.Parsaeimehr@gmail.com
Elmira Sargsyan, G. S. Davtyan Institute of Hydroponics Problems, National Academy of Sciences Republic of Armenia, Yerevan, 375082, e-mail: Elmira_sargsyan14@yahoo.com
Anush Vardanyan, G. S. Davtyan Institute of Hydroponics Problems, National Academy of Sciences Republic of Armenia, Yerevan, 375082, e-mail: Anushikv74@yandex.ru.
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