



Article

HUSSAIN, M.I.^{1,2}
QAMAR ABBAS, S.^{3,4}
REIGOSA, M.J.¹

ACTIVITIES AND NOVEL APPLICATIONS OF SECONDARY METABOLITE COUMARINS

Atividades e Novas Aplicações das Cumarinas Enquanto Metabólitos Secundários

ABSTRACT - This review covers biological activity of secondary metabolites, coumarin and their derivatives on different organisms (pests, pathogens, weeds), as well as their applications in agriculture as eco-friendly pesticides and weed control agents. Naturally occurring coumarins have shown biological and allelopathic potential on a broad range of organisms. Coumarin inhibits seed germination, root growth, morphology, histology, water uptake, respiration, photosynthesis, cell elongation, cell division and differentiation. Coumarin demonstrate excellent insecticidal potential against eggs, larvae and adult insects. Coumarin showed antifeedent responses in a wide range of members from invertebrates to vertebrates. The information provided in this review also shed light on further research and development of coumarin and its derivatives as potential plant protection lead compounds to control weeds and harmful pests.

Keywords: coumarin, secondary metabolites, multifunctionality, herbivory, allelopathy, phytotoxicity, weed control.

RESUMO - Esta revisão da literatura abrange a atividade biológica da cumarina enquanto metabólito secundário e seus derivados em diferentes organismos (pragas, agentes patogênicos, plantas daninhas), bem como suas aplicações na agricultura como pesticidas ecológicos e agentes de controle de plantas daninhas. As cumarinas de ocorrência natural mostraram potencial biológico e alelopático em uma ampla gama de organismos. A cumarina inibe a germinação das sementes, o crescimento radicular, a morfologia, a histologia, a absorção de água, a respiração, a fotossíntese, o alongamento celular, a divisão celular e a diferenciação. Além disso, ela demonstra excelente potencial inseticida contra ovos, larvas e insetos adultos, tendo apresentado resposta antialimentar em ampla gama de membros de invertebrados e vertebrados. As informações contidas nesta revisão também evidenciam novas pesquisas e o desenvolvimento da cumarina e seus derivados como potenciais compostos protetores de plantas para controle de plantas daninhas e pragas prejudiciais.

* **Corresponding author:**
<mih76@uvigo.es>

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Palavras-chave: cumarina, metabólitos secundários, multifuncionalidade, herbivoria, alelopatia, fitotoxicidade, controle de plantas daninhas.

¹ University of Vigo, Campus Lagoas-Marcosende, 36310-Vigo, Spain; ² Institute of Science & Engineering, University of Sharjah, P.O. Box 27272, Sharjah, U.A.E.; ³ Universitat Autònoma de Barcelona, Bellaterra, Cerdanyola del Valles, 08193-Barcelona, Spain; ⁴ University of Agriculture, Faisalabad, Pakistan.

INTRODUCTION

Phytochemicals demonstrate diverse responses against pathogens, insects, pests, human diseases and predators. They are phytotoxic in nature and repellent to herbivores; moreover, many of them are also involved in the defense against abiotic stress (Hadacek et al., 1994). Natural compounds are a source of new class of plant based secondary metabolites, as well as ecologically and toxicologically safer molecules than many synthetic chemical compounds. Coumarins are a class of lactone molecules which have a benzene ring fused to α -pyrone ring, and essentially possess a conjugated system with electron-rich and good charge-transport properties (Murray, 1997). Coumarins have been reported to exhibit several biological activities with a wide range of applications (Matos et al., 2012; Zheng et al., 2013). Coumarins are reported to be present in various cosmetics and industrial additives, and their derivatives have been used as aroma enhancers in tobacco and certain alcoholic drinks (Fais et al., 2009; Matos et al., 2013). More than 1300 coumarins isolated from plants, bacteria, and fungi have been identified as secondary metabolites (Iranshahi et al., 2009). In 1822, Vogel isolated and purified coumarin from tonka bean (*Dipteryx odorata*). Several coumarin compounds have been reported in Rutaceae and Apiaceae families (Hadacek et al., 1994; Ganzera et al., 1997). Because of their wide biological activities, several coumarin compounds are reported to be health-promoting constituents of herbal and medicinal plant preparations. Several reviews have summarized and highlighted new frontiers in the application of coumarins, especially concerning their antioxidant (Thuong et al., 2010), antimycobacterial (Schinkovitz et al., 2003), anticoagulant, antitumoral, antiviral, antifungal, and antiinflammatory activities (Garcia-Argaez et al., 2000; Epifano et al., 2010; Riveiro et al., 2010).

Based on the diverse biological activities, this review provides a general overview of the origin, sources, and biological activities of coumarins, and a brief discussion on the most important mode of action of these secondary metabolites in different organisms. Finally, the biological activities of coumarins that are of interest in agriculture and plant production, as well as the potential novel applications of coumarins in agricultural systems, will be also reviewed.

Coumarins

Coumarins have been distributed in several plant families including; *Apiaceae*, *Rutaceae*, *Asteraceae*, *Fabaceae*, *Oleaceae*, *Moraceae*, and *Thymelaeaceae* (Ribeiro and Kaplan 2002). Coumarins have shown to be present in seeds, roots, stems, flowers, leaves, and fruits, although the highest concentrations are reported in flowers and fruits (Venugopala et al., 2013). Coumarin was also isolated from microorganisms and sponges (De Lira, 2007). They are produced from phenylalanine via shikimate biosynthesis (Dewick, 2002). Coumarin derivatives can be classified as simple coumarins, furocoumarins, dihydrofurocoumarins, pyranocoumarins (linear and angular), phenylcoumarins, and biscoumarins (Venugopala et al., 2003; Borges et al., 2009). Major coumarin constituents isolated from plants include: simple hydroxycoumarins, furocoumarins and isofurocoumarins, pyranocoumarins, biscoumarins, and dihydroisocoumarins (Venugopala et al., 2013). Coumarins from *Peucedanum ostruthium*, most notably ostruthol, have also been shown to act as inhibitors of acetylcholinesterase, which implicates a high potential for the treatment of Alzheimer's disease (Urbain et al., 2005).

Biosynthesis, structure and roles of Coumarins in nature

Simple coumarins are biogenetically derived from shikimic acid, via cinnamic acid. The specificity of the process is C-2 hydroxylation, producing a break (β -oxidation) of the side chain (*Salix* spp.), or chain isomerization and subsequent lactonization, generating umbelliferone. Figure 1 shows the entire process (Dewick, 2002). Pyrano and furocoumarins are also biogenetically derived from shikimic acid. These coumarins can be divided into two groups – linear and angular – depending on the position where the isopentenyl pyrophosphate is condensed to further cyclize and form the heterocycle. An approximation for the dicoumarol biogenesis is the hydroxylation of the 4-position of coumarin, which then captures a molecule of formaldehyde and is condensed

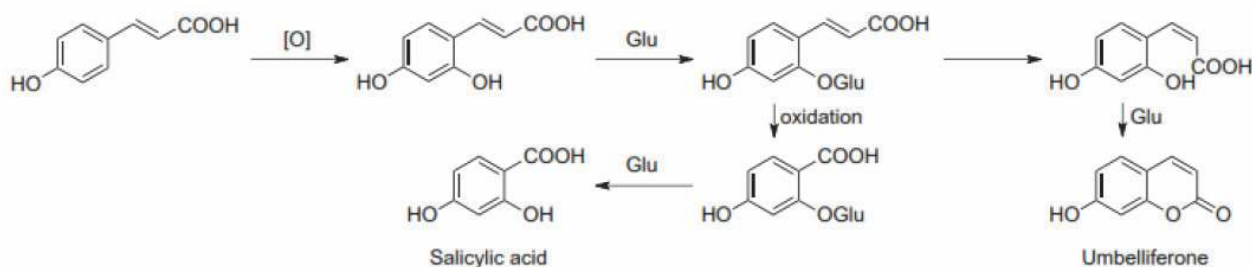


Figure 1 - Biosynthesis of simple coumarins.

with another molecule of 4 hydroxycoumarin, and finally enolizes the keto group that forms dicumarol (Dewick, 2002). Simple coumarins are common in all angiosperms (e.g. *Oleaceae* and *Asteraceae*) (Ribeiro and Kaplan, 2002). Plant family *Apiaceae* is the major and one of the most diverse sources of coumarins, containing five different types of coumarin derivatives (simple coumarins, lineal furocoumarins, angular furocoumarins, lineal pyranocoumarins, and angular pyranocoumarins). *Rutaceae* is also highlighted in both occurrence and diversification. Generally, the division *Angiospermae* is preferably rich in simple coumarins, followed by the furo and pyranocoumarins (Ribeiro and Kaplan, 2002).

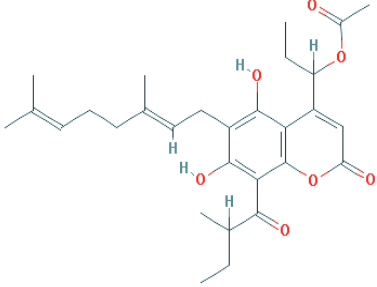
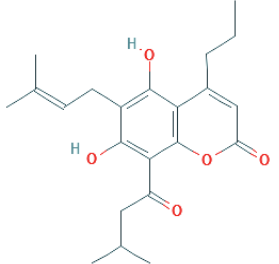
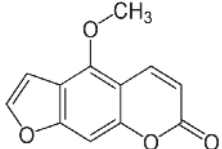
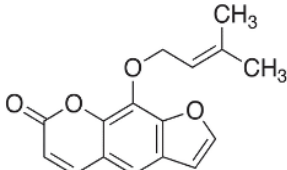
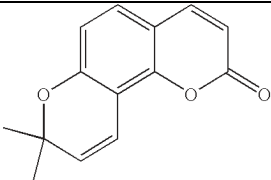
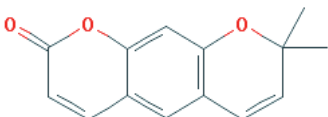
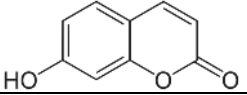
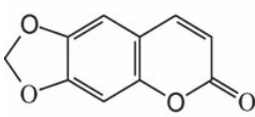
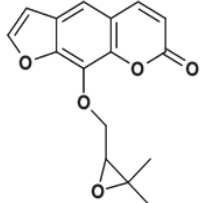
A large number of valuable species used commonly as medicinal plants, aromatic plants, and edible plants for human and animal feeding belongs to coumarin-rich plant families. There are several families with certain coumarin containing plant species; a historical record of ethnomedicinal use in *traditional medicine systems*, Ayurveda Medicine, Traditional Chinese Medicine and Unani Medicine. Previously, various pharmaceutical characteristics of coumarin have also been reported (Kostova, 2007, Zheng et al., 2013; Venugopala et al., 2013), which include anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer, anti-hypertensive, antitubercular, anticonvulsant, anti-adipogenic, antioxidant, and neuroprotective properties. Several reviews have summarized and highlighted advances in the application of coumarins, especially as regards their antioxidant and anti cancer properties (Hayes et al., 1998; Galvano et al., 2001; Fylaktakidou et al., 2004; Rietjens et al., 2005; Riveiro et al., 2010). The great structural diversity of coumarin and their derivatives allows for several novel applications in agriculture and plant protection (Table 1).

Table 1 - Chemical structures and biological activities of some coumarins of importance for agriculture and plant protection

Structure	Chemical name	Biological activities
	Ostruthol: [(2R)-3-hydroxy-3-methyl-1-(7-oxofuro[3,2-g]chromen-4-yl)oxybutan-2-yl] (Z)-2-methylbut-2-enoate	Phytotoxic (Urbain et al., 2005)
	Scopoletin: 7-hydroxy-6-methoxy, 2H-1-Benzopyran-2-one	Antifeedant (Barrero et al., 2013; Tripathi et al., 2011), Insecticidal (Sharma et al., 2006)

To be continued ...

Table 1, cont.

Structure	Chemical name	Biological activities
	Surangin B: 1-[6-[(2E)-3,7-dimethylocta-2,6-dienyl]-5,7-dihydroxy-8-(2-methylbutanoyl)-2-oxochromen-4-yl]propyl acetate	Antifeedant (Issakul et al., 2011), Phytotoxic (Nicholson, 1994)
	Mamea B/BA: 5,7-dihydroxy-8-(3-methylbutanoyl)-6-(3-methylbut-2-enyl)-4-propylchromen-2-one	Insecticidal (Mungkornasawakul, 2004; Mahidol et al., 2002)
	Bergapten: 5-Methoxypsoralen	Phytotoxic (Hadaček et al., 1994)
	Imperatorin: 8-Isopentenylloxypsoralene	Insecticidal (Hadaček et al., 1994)
	Seselin: 8,8-Dimethyl-2H,8H-pyrano[2,3-f]chromen-2-one	Insecticidal (Mukandiwa et al., 2013)
	Xanthyletin: 2,2-dimethylpyrano[3,2-g]chromen-8-one	Insecticidal (Vera et al., 2006)
	Umbelliferone: 7-hydroxychromen-2-one	Antifungal (Rahman, 2000)
	Ayapin: 6H-1,3-Dioxolo(4,5-g)(1)benzopyran-6-one	Antifungal (Prats et al., 2007; Yoshikawa et al., 1979)
	Heraclenin: 9-[[2R)-3,3-dimethyloxiran-2-yl]methoxy]furo[3,2-g]chromen-7-one	Nematocidal (Wang et al., 2008)

Chemical ecology of coumarins

The chemical ecology of coumarins is multifaceted (Figure 2). Many aspects such as responses to ecological factors, antifeedant activity, ecophysiological crosstalks, allelopathic effects, phytotoxic impact on agricultural crops and weeds, insecticidal behavior, antioxidant functions of coumarins are summarized in the following sections.

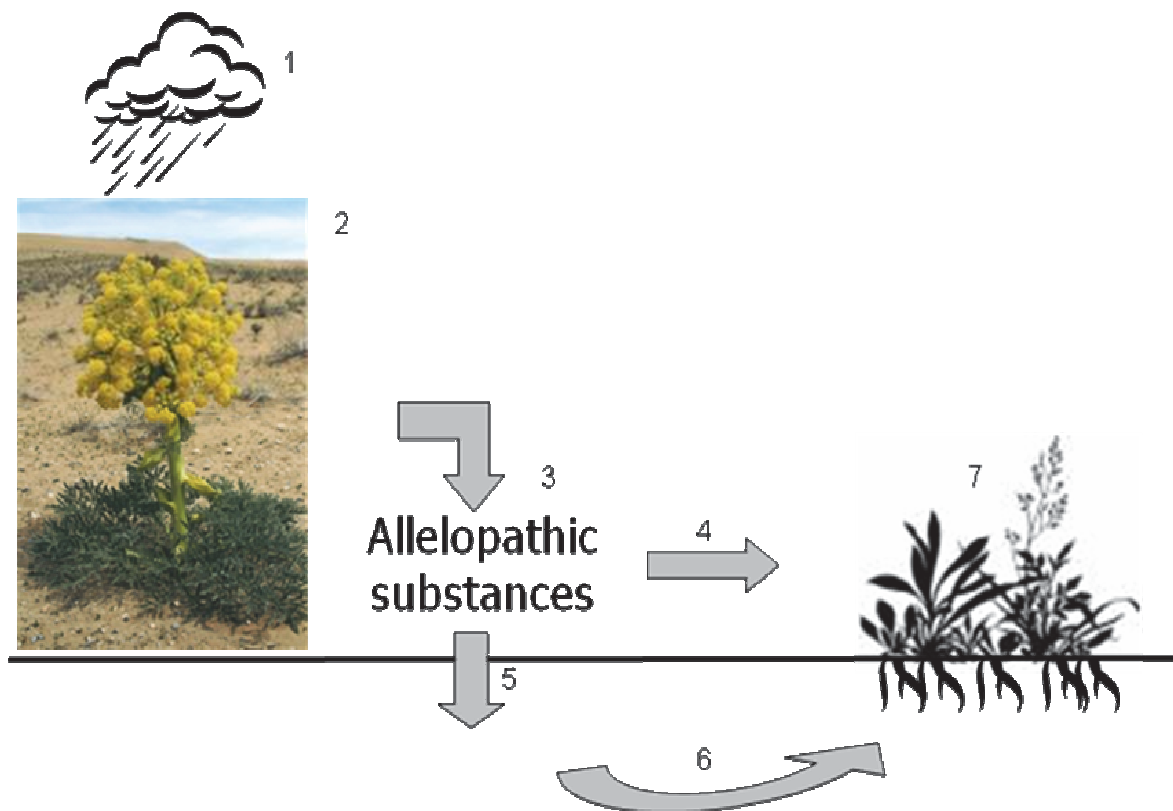


Figure 2 - A schematic presentation of allelopathic plant (*Ferula dseudalliacea*), its secondary metabolites (SM), release and transport of SMs into the surrounding environment and impact on target weeds and plants.

Variations of coumarins derived compounds in response to ecological factors

In an interesting study, Castro et al. (2006) found that plants grown under impacts of different radiation levels and photoperiods exhibited higher levels of coumarin than non-treated plants of *Mikania glomerata* Sprengel (Asteraceae). Photoperiod significantly increased coumarin content in *M. glomerata* leaves and stems, which showed higher coumarin % at all levels of radiation. Pereira et al. (1998) reported the impact of fertilization on biomass yield and coumarin content in *M. glomerata* under organic (humus or manure) and nitrogen fertilizer treatments for one year. Coumarin concentrations were increased by organic fertilization, and inorganic nutrients induced increased phytomass (stem and leaf) yield; however, non-fertilized plants showed enhanced leaf production. Ramakrishna and Ravishankar (2011) reported that environmental factors viz. temperature, humidity, light intensity, water supply, minerals, and CO₂ influenced plant growth and production of secondary metabolites, including coumarin.

Antifeedant activity of coumarins

The feeding-deterrent property is an important function of coumarin in mediating plant-animal interactions. Coumarin has a deterrent effect on a large spectrum of organisms from invertebrates to vertebrates. The leaves of *Clausena anisata* are used traditionally to expel maggots

from wounds of animals in Zimbabwe. At relatively low concentrations (1 ppm), coumarin (acetone extract of *C. anisata* leaf powder (containing pyranocoumarin, seselin) inhibited feed intake in the first and second instars of blowfly larvae and resulted in significantly lower mass pupae (Mukandiwa et al., 2013). However, the mode of action of coumarin as an antifeedant insect is yet to be comprehensively studied. Vera et al. (2006) studied the phagodepression activity of different coumarins (2H-1-benzopyran-2-ones), 6 hydroxy-7-isoprenyloxycoumarin, 6-methoxy-7-isoprenyloxycoumarin, 6,7-methylenedioxy coumarin, 5-methoxy-6,7-methylenedioxy coumarin, 6-methoxy-7-(2-hydroxyethoxy) coumarin *Pterocaulon polystachyum* and tested their anti-feedent role against *Spodoptera frugiperda* (Lepidoptera: Noctuidae) larvae. They concluded that larval growth rate during early larval instars and pupal growth was significantly reduced by all coumarin treatments.

It was found that phytochemicals, including coumarin isolated from *Artemisia granatensis*, were responsible for the antifeedant effects against *Spodoptera littoralis*, *Myzus persicae* and *Rhopalosiphum padi* (Barrero et al., 2013). Methoxy coumarin (scopoletin) from the stem part of *Artemisia annua* showed feeding deterrence and growth inhibitory potential against the noxious lepidopteran insect *Spilartctia obliqua* Walker. Scopoletin gave feeding deterrence of 50% (FD₅₀) value of 96.7 µg g⁻¹ diet when mixed into an artificial diet. *Spodoptera obliqua* larvae (12-day-old) exposed to the highest concentration (250 µg g⁻¹ diet) of scopoletin showed 77.1% feeding-deterrence (Tripathi et al., 2011). Surangin B isolated from *M. siamensis* showed high anti-feedant toxicity to the 3rd instar larvae of *P. xylostella* L. (diamondback moth) with a very low percentage of damaged leaf area of 0.83 and 0.14% at the concentrations of 0.5 and 1.0 mg mL⁻¹, and it proved to be better than methomyl (used as a conventional insecticide) (Issakul et al., 2011). It was concluded that surangin B expressed stronger toxicity to diamondback moths than methomyl. It was demonstrated that mitochondrial blockade (leading to bio-energetic failure in muscles and nerves) was a major mechanism in the development of paralysis in insects exposed to surangin B (Nicholson, 1994).

Allelopathic effects of coumarins

Allelopathy is an emerging branch of applied science which studies any process primarily involving secondary metabolites produced by plants, algae, bacteria, and fungi which influence the growth and development of biological and agricultural systems, producing both positive and negative effects (IAS, 1996). Allelochemicals enter the soil rhizosphere in a number of ways – such as plant degradation, volatilization, leaching from plant leaves, and root exudation – and affect the growth, physiological processes and biochemical traits of surrounding plants. Their continuous presence in the field is important for weed suppression when allelopathic crops are used as cover crops, mulch, smother crops, green manure, or grown in rotational sequences and can be exploited by industry led discovery programs (Hussain and Reigosa, 2011; Macias et al., 2014; Nuria et al., 2014; Rials et al., 2014; Hussain et al., 2015; Hussain and Reigosa, 2017). Many shrubs and exotic invasive trees exhibit allelopathy against other plants and weeds and some of them (particularly invasive plants) have developed allelopathy as a successful strategy for establishment in a new environment (Duke, 1986; Hussain et al., 2011). Not only living plants, but also weed residues that remain in the soil after completions of life cycles are inhibitory in nature. They interfere with soil characteristics, add significant amount of allelochemicals during decomposition, deteriorate soil quality and reduce crop yield (Abbas et al., 1995). Ripe fruits of *Solanum* often contain glycoalkaloids that possess multiple biological activities, e.g., germination inhibition, laxative effects on mammals, constipating effects on birds, deterrent effects on herbivores, etc. (Abbas et al., 1996). Many alkaloids simultaneously exhibit allelopathic, antibacterial and animal toxicity effects (Lee et al., 1997). Among plant phenolics, coumarins are widely distributed in natural plant communities and are potent allelopathic agents (Razavi, 2011).

Weed Management

The overuse of synthetic agrochemicals for pest and weed control has increased environmental pollution, the use of unsafe agricultural products and human health concerns.

Furthermore, herbicide resistant weeds have become more common over the last 20 years (Scarabel et al., 2007). The possible use of plant secondary metabolites as herbicides has long been discussed (Macias et al., 2007). Despite considerable study of this topic, few herbicides and herbicide classes have been previously reviewed (Duke et al., 2002).

COUMARIN USES IN AGRICULTURE

Germination and seedling growth inhibition

Coumarins (7-prenyloxy coumarin, auraptene; $<100 \mu\text{g mL}^{-1}$ concentrations) are phytotoxic and showed significant inhibition of germination, seedling growth and root/shoot growth of lettuce (Razavi and Zarrini, 2010). Chuah et al. (2013), studied the effectiveness of selected non-ionic surfactants (NIS) and an organosilicon (OS) + *p*-vanillin and demonstrated phytotoxicity of the phenolic mixture which reduced the germination and seedling growth of *Eleusine indica* (biotypes are increasing their resistance to various groups of herbicides) Abenavoli et al. (2010), conducted an experiment on seven-day-old maize seedlings grown in a nitrogen-free hydroponic culture and exposed them for 48 h to 0, 100 and 300 μM trans-cinnamic, *p*-coumaric, ferulic, caffeic acids, umbelliferone and 200 μM KNO_3 . Net nitrate uptake and plasma membrane H^+ -ATPase activity significantly decreased in a concentration-dependent manner in response to trans-cinnamic, ferulic and *p*-coumaric acids, while umbelliferone and caffeic acid had no effect on H^+ -ATPase activity. Chuah et al. (2013) demonstrated that seed germination, water uptake, electrolyte retention capacity, and O_2 consumption were significantly reduced in durum wheat (*Triticum = turgidum* ssp. durum Desf.) following coumarin treatment.

Coumarin as cell division and cell elongation inhibitor

Coumarin inhibits cell elongation, cell division, differentiation, rhizogenesis and germination (Kupidlowska et al., 1994a), and promotes rooting in leaf explants of petunia (Abenavoli et al., 2001b). Coumarin and xanthotoxin stimulated the fragmentation of endoplasmic reticulum cisternae, decreased the number of dictyosomes and condensed the mitochondrial matrix indicating a possible energy shortage in the maize cell and cucumber plants while the garden pea was resistant (Francisco et al., 1991; Kupidlowska et al., 1994b).

Impact on photosynthesis and reactive oxygen species

It was also argued that coumarin decreases respiration and photosynthesis in intact plants by inhibiting electron transport, (Kupidlowska et al., 1994b) and the activity of enzymes responsible for nitrogen metabolism in carrot cell suspension culture (Abenavoli and Fuggi, 1995). Antonio et al. (2013), reported a strong correlation between reactive oxygen species generation, distribution and coumarin-mediated recovery of root gravitropism in *Arabidopsis thaliana*. In another study, Antonio et al. (2010), studied the short-term effects of coumarin on three different maize primary root zones, transition zone (TZ, 3 mm), and two non-growing zones (NGZ1 and NGZ2 at 20 and 50 mm). They concluded that primary maize root was sensitive to coumarin within a 20 mm section from the root tip, but more distal NGZ2 zone was not involved in coumarin-elicited physiological responses.

Coumarin delayed the reactivation of peroxidases, enhanced the activity of superoxide dismutase, decreased the activities of selected marker enzymes for metabolic resumption, and repressed the transcription of molecular chaperons involved in secretory pathways (Abenavoli et al., 2006). Exposure of carrot to micromolar levels of coumarin caused severe inhibition of cell growth, accumulation of free amino acids, ammonium in the cultured cells, and stimulated the glutamine synthetase, glutamate dehydrogenase, malate dehydrogenase, glucose-6-phosphate dehydrogenase and phosphoenolpyruvate carboxylase activities of cultured cells (Abenavoli et al., 2003). Coumarin induces metabolic and morpho-functional changes in *Petunia hybrida* leaf explants. Tissues grown in the presence of coumarin show long roots with few root hairs. However, leaf explants grown with indoleacetic acid have short roots with abundant root hairs. The presence of both indoleacetic acid and coumarin induces long roots with numerous root hairs. The presence

of both indoleacetic acid and coumarin induces long roots with numerous root hairs and IAA-oxidase activity remains low in the culture tissues treated with coumarin (Abenavoli et al., 2001a). Dastan et al. (2014) found that coumarins isolated from the roots of *Ferula pseudalliacea* (Sanandajin) (Figura 2) remarkably inhibited seed germination of all tested weeds and plants.

It was reported that coumarin, at all the concentrations tested, was able to increase net nitrate uptake upon full induction and only 0.1 mM coumarin significantly increased the rate of induction. This concentration of coumarin might have been the most effective because it caused subapical swelling of the tip, thereby increasing the root surface available for nitrate absorption. It was argued that coumarin stimulates net nitrate uptake (Abenavoli et al., 2001b). They concluded that coumarin was the main compound responsible for root growth inhibition as well as changes in histology and morphology of roots. Abenavoli et al. (2004) found that maize seedlings grew in a hydroponic culture for 6 days, and then added coumarin (at concentrations of 0, 25, 100, and 400 μM) to the nutrient solution. They showed that the coumarin inhibited root length but the effects differed, depending on root type. Abenavoli et al. (2008) applied non-linear regression analysis to assess the phytotoxicity of trans-cinnamic acid, umbelliferone and coumarin on the whole root system of *Arabidopsis thaliana* and on the component root types (primary root and lateral roots). At low concentrations, coumarin induced a hormetic effect on root elongation both in the whole root system and also on the lateral roots but not on primary root. This confirms coumarins have a selective effect on particular root types. Inhibition of root growth could have been caused by a coumarin induced interference with auxin metabolism and subcellular distribution. Anya et al. (2005) reported that coumarin inhibits photosynthetic phosphorelation in a dose-dependent manner. The IC_{50} value for imperator in inhibitory effects on ATP synthesis in spinach chloroplasts was calculated as $7.15 \mu\text{g m L}^{-1}$. In another study, coumarin, trans-cinnamic acid, o-coumaric acid, and hydro-cinnamic acid at 10^{-4} M significantly reduced root lengths of alfalfa and barnyard grass (Chon et al., 2002).

Insecticidal activity of coumarin

Insect pest management is nowadays a worldwide ecological challenge mainly as a result of environmental pollution caused by extensive use of synthetic chemical pesticides (Rattan, 2010). A cursory analysis of the impact of natural products on various categories of insect/pests reveals the remarkable contributions they have had on the agricultural insecticide market. Synthetic insecticides based on natural products have been around for decades and the impact is most evident when looking at pyrethroids and neonicotinoids. Such products and their acceptance by both consumers and farmers will continue to drive us towards even better unmodified natural product insecticides. Plants are a good potential source of such compounds, since many plant species have a defense mechanism and produce secondary metabolites in order to survive in the ecosystem. The plant families Asteraceae (Chiasson et al., 2001; Gonzalez-Coloma et al., 2005), Milliaceae (Gupta and Misra, 2006; Prasad et al., 2006; Sharma et al., 2006), and Apiaceae (Kang et al., 2006) are known to have insecticidal constituents. In sunflower, it was demonstrated that feeding damage of the plant by sunflower beetle *Zygogramma exclamationis* induced coumarin biosynthesis. The concentration of scopoletin was 3-5 times higher in the damaged plant and control. Induced coumarin subsequently deters feeding of sunflower beetles (Olson and Roseland, 1991). Other researchers have also shown that coumarin exhibited strong insecticidal activity and caused high percentage of mortality of eggs and larvae of insects (Sharma et al., 2006). Four coumarins isolated from the crude seed extract of *Mammea siamensis* – surangin B, surangin C, mammea E/BB and mammea E/BC - were reported to have insecticidal properties (Mungkornasawakul, 2004). Mahidol et al. (2002) found 4 new *Mammea* coumarins isolated from the flowers of *M. siamensis* – mammea E/BA cyclo D, mammea E/BC cyclo D, mammea E/BD cyclo D, and mammea E/AC cyclo D. The insecticidal properties of *mammea* have been described by many investigators and the active compounds were usually coumarins.

Mammein, the insecticidal compound from the seeds of *Mammea americana*, was the first naturally occurring coumarin with a *n*-propyl substituent at C-4, (Morris and Pagan, 1953), whereas mammeisin was isolated from the fruits peels of *M. americana* (Finnegan et al., 1961). Crombie et al. (1972) reported 4-alkyl-5-7-dihydroxy coumarins namely, mammea E/BA and mammea E/BB, which also displayed insecticidal activities. The insecticidal activity of various

parts of the mammea tree was studied and it was evident in both feeding and contact experiments that the seed kernel extract was the most effective part against armyworms, melonworms, cockroaches, ants, drywood termites, mosquitoes and their larvae, flies, aphids and the larvae of diamondback moths (Morton, 1987). *M. siamensis* was highly effective against the fourth-instar larvae of *Aedes aegypti* with a LC_{50} value of $5.9 \mu\text{g L}^{-1}$ (Promsiri et al., 2006). The insecticidal substances extracted from *M. siamensis* and reported the insecticidal effects of ethanolic crude extract of *M. siamensis* on the eggs of the housefly, *Musca domestica* (Issakul et al., 2004). Hadacek et al. (1994) studied the insecticidal activity of 17 coumarins present in *Peucedanum arenarium*, *P. austriacum*, *P. coriaceum*, *P. longifolium*, *P. officinale* L., *P. oreoselinum*, *P. ostruthium* L., and *P. palustre* against *Spodoptera littoralis* (Boisduval) (Lepidoptera: Noctuidae). Most linear furanocoumarins and the angular dihydrofuranocoumarin athamantin were active. Oxygenation of the prenyl residue of linear furanocoumarins decreased their activity and further esterification with angelic acid lead to inactivity. In a dietary utilization bioassay, five linear furanocoumarins (bergapten, isopimpinellin, imperatorin, peucedanin and 8-methoxypeucedanin) decreased the relative growth rate and relative consumption rate of treated larvae (Hadacek et al., 1994). Coumarin is also regarded as an ovicide agent (Nakajima and Kawazu, 1980). It was also demonstrated that some psoralen derivatives, such as 8-methoxy, 5-methoxy and 5, 8-dimethoxy psoralen, were regarded as insect antifeedant agents (Stevenson et al., 2003). Thus, the development of plants using genetic engineering producing coumarins may be a novel approach to control herbivorous insects.

Overall, coumarins (natural or derivatives) are highly phytotoxic and their performance in controlling insects, pests and for weed management has shown very promising results. However, further research in the field is required on the mode of action and biological impact of coumarin on pests and resistant weeds. Here, we emphasized the promising biological activities of coumarin as fungicides, insecticides, phytotoxic and plant growth regulators; however, more research is needed to fully understand the molecular mechanisms involved.

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REFERENCES

- Abbas H.K. et al. Susceptibility of various crop and weed species to AAL-toxin, a natural herbicide. **Weed Technol.** 1995;9:125-30.
- Abbas H.K., Duke S.O., Shier W.T., Riley R.T., Kraus G.A. The chemistry and biological activities of the natural products AAL-Toxin and the Fumonisin. In: Singh B.R., Tu A.T. editors. **Natural toxins 2**. Advances in experimental medicine and biology. Boston: Springer, 1996. v.391. p.293-308
- Abenavoli M.R. et al. Allelochemical effects on net nitrate uptake and plasma membrane H⁺-ATPase activity in maize seedlings. **Biol Plant.** 2010;54:149-53.
- Abenavoli M.R. et al. Coumarin differentially affects the morphology of different root types of maize seedlings. **J Chem Ecol.** 2004;30:1871-83.
- Abenavoli M.R. et al. Coumarin inhibits the growth of carrot (*Daucus carota* L. cv. Saint Valery) cells in suspension culture. **J Plant Physiol.** 2003;160:227-37.
- Abenavoli M.R. et al. Effects of different allelochemicals on root morphology of *Arabidopsis thaliana*. **Allelop J.** 2008;22:245-50.
- Abenavoli M.R. et al. Influence of coumarin on the net nitrate uptake in durum wheat. **New Phytol.** 2001a;150:619-27.
- Abenavoli M.R. et al. The inhibitory effects of coumarin on the germination of durum wheat (*Triticum turgidum* ssp. *durum*, cv. Simeto) seeds. **J Chem Ecol.** 2006;32:489-506.

- Abenavoli M.R., Fuggi A. Effect of coumarin on growth of cells cultured in liquid medium from carrot (*Daucus carota* L.). **Giorn Bot Ital.** 1995;129:989-90.
- Abenavoli M.R., Sorgona A., Muscolo A. Morphological changes in tissue culture of *Petunia hybrida* in response to coumarin allelochemical. **Allelop J.** 2001b;8:171-7.
- Antonio L. et al. Gravitropic response induced by coumarin: Evidences of ROS distribution involvement. **Plant Sig Behav.** 2013;8:2 e23156.
- Antonio L. et al. Short-term effects of coumarin along the maize primary root axis. **Plant Sign Behav.** 2010;5:1395-4000.
- Anya A.L. et al. Allelochemicals from *Staurantus perforatus*, a Rutaceae tree of the Yuctan Peninsula, Mexico. **Phytochemistry.** 2005;66:487-94.
- Barrero A.F. et al. Terpenes and polyacetylenes from cultivated *Artemisia granatensis* boiss (Royal chamomile) and their defensive properties. **Phytochemistry.** 2013;94:192-7.
- Borges F. et al. Simple coumarins: Privileged scaffolds in medicinal chemistry. **Front Med Chem Biol Inter.** 2009;4:23-85.
- Chiasson H. et al. Acaricidal properties of *Artemisia absinthium* and *Tanacetum vulgare* (Asteraceae) essential oils obtained by three methods of extraction. **J Econ Entomol.** 2001;94:167-71.
- Chon S.U. et al. Effects of alfalfa leaf extracts and phenolic allelochemicals on early seedling growth and root morphology of alfalfa and barnyard grass. **Crop Protec.** 2002;21:1077-82.
- Chuah T.S., Tan P.K., Ismail B.S. Effects of adjuvants and soil microbes on the phytotoxic activity of coumarin in combination with *p*-vanillin on goosegrass (*Eleusine indica* L.) seedling emergence and growth. **South Afr J Bot.** 2013;84:128-33.
- Crombie L. et al. Extractives of *Mammea americana* L. Part V. The insecticidal compounds. **J Chem Soc Perkin Trans.** 1972;1:2255-60.
- Dastan D. et al. Phytotoxicity and cytotoxicity of disesquiterpene and sesquiterpene coumarins from *Ferula pseudalliacea*. **Indian Crops Prod.** 2014; 55:43-8.
- Castro E.M. et al. Coumarin contents in young *Mikania glomerata* plants (Guaco) under different radiation levels and photoperiod. **Acta Farm Bonaer.** 2006;25:387-92.
- De Lira S.P. et al. A SARS-coronavirus 3CL protease inhibitor isolated from the marine sponge *Axinella* cf. *corrugata*: structure elucidation and synthesis. **J Braz Chem Soc.** 2007;18:440-3.
- Dewick P.M. **Medicinal natural products: A biosynthetic approach.** 2nd. ed. New York: John Wiley, 2002.
- Duke S.O. et al. Chemicals from nature for weed management. **Weed Sci.** 2002;50:138-51.
- Duke S.O. Microbial phytotoxins as herbicides - a perspective. In: Putnam A.R., Tang C.S., editors. **The science of allelopathy.** New York: John Wiley, 1986. p.287-304.
- Epifano F., Curini M., Genovese S. Prenyloxyphenylpropanoids as a novel class of anti-inflammatory agents. **Antiinflamm Allerg Agents Med Chem.** 2010;9:158-65.
- Fais A. et al. Tyrosinase inhibitor activity of coumarin-resveratrol hybrids. **Molecules.** 2009;14:2514-20.
- Finnegan R., Morris M., Djerassi C. Naturally occurring oxygen Heterocyclics. X.¹ 4-Phenyl-5,7-dihydroxy-6-isovaleryl-8-isopentenylcoumarin. **J Org Chem.** 1961;26:1180-4.
- Francisco J., Pérez J., Juan O.N. Root exudates of wild oats: Allelopathic effect on spring wheat. **Phytochemistry.** 1991;30:2199-202.
- Fylaktakidou K.C. et al. Natural and synthetic coumarin derivatives with anti-inflammatory/antioxidant activities. **Curr Pharm Des.** 2004;10:3813-33.
- Galvano F. et al. Dietary strategies to counteract the effects of mycotoxins: A review. **J Food Prot.** 2001;64:120-31.

- Ganzera M., Sturm S., Stuppner H. HPLC-MS and MECC analysis of coumarins. **Chromatographia**. 1997;46:197-203.
- Garcia-Argaez A.N. et al. Anti-inflammatory activity of coumarins from *Decatropis bicolor* on TPA ear mice model. **Planta Med.** 2000;66:279-81.
- Gonzalez-Coloma A. et al. Antifeedant/insecticidal terpenes from Asteraceae and Labiatae species native to Argentinean semi-arid lands. **Z Naturforsch C J Biosci.** 2005;60:855-61.
- Gupta S.C., Misra A.K. Management of okra shoot of fruit borer, *Earias vittella fabr.* through bio-rational insecticides. **Pestic Res J.** 2006;18:33-4.
- Hadacek F. et al. Analysis, isolation and insecticidal activity of linear furanocoumarins and other coumarin derivatives from Peucedanum (Apiaceae: Apioideae). **J Chem Ecol.** 1994; 20:2035-54.
- Hayes J.D. et al. Regulation of rat glutathione S-transferase A5 by cancer chemopreventive agents: mechanisms of inducible resistance to aflatoxin B1. **Chem Biol Inter.** 1998;111-112:51-67.
- Hussain M.I. et al. Ecophysiological responses of native plants to phytotoxic effect of *Acacia melanoxylon* R. Br. **Agrofor Syst.** 2011;83:149-66.
- Hussain M.I., Reigosa M.J. A chlorophyll fluorescence analysis of photosynthetic efficiency, quantum yield and fractions of photon energy in PSII antennae of *Lactuca sativa* exposed to cinnamic acid. **Plant Physiol Biochem.** 2011;49:1290-8.
- Hussain M.I., Reigosa M.J., Al-Dakheel A.J. Biochemical, physiological and isotopic responses to natural product *p*-hydroxybenzoic acid in Cocksfoot (*Dactylis glomerata* L.). **Plant Growth Regul.** 2015;75:783-92.
- Hussain M.I., Reigosa M.J. Evaluation of photosynthetic performance and carbon isotope discrimination in perennial ryegrass (*Lolium perenne* L.) under allelochemicals stress. **Ecotoxicology.** 2017;26:613-24.
- International Allelopathy Society – IAS. First World Congress on Allelopathy: A Science for the future. Cadiz: 1996.
- Iranshahi M. et al. Evaluation of antioxidant, anti-inflammatory and lipoxygenase inhibitory activities of the prenylated coumarin umbelliprenin. **Daru.** 2009;17:99-103.
- Issakul K. et al. Insecticidal effectiveness of compounds from *Mammea siamensis* Kost. against *Musca domestica* Linn. **Acta Hort.** 2004;629:103-7.
- Issakul K. et al. Potential of *Mammea siamensis* as a botanical insecticide: Its efficiency on diamondback moth and side effects on non-target organisms. **J Med Plants Res.** 2011;5:2149-56.
- Kang S. et al. Toxicity of bisabolangelone from *Ostericum koreanum* roots to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (Acari: Pyroglyphidae). **J Agric Food Chem.** 2006;54:3547-50.
- Kostova I. Studying plant derived coumarins for their pharmacological and therapeutic properties as potential anticancer drugs. **Expert Opin Drug Discov.** 2007;2:1605-18.
- Kupidlowska E. et al. Effect of coumarin and xanthotoxin on mitochondrial structure, oxygen uptake, and succinate dehydrogenase activity in onion root cells. **J Chem Ecol.** 1994a;20:2471-80.
- Kupidlowska E. et al. The effect of coumarins on root elongation and ultrastructure of meristematic cell protoplasts. **Ann Bot.** 1994b;73:525-30.
- Lee D.L. et al. The discovery and structural requirements of inhibitors of *p*-hydroxyphenylpyruvate dioxygenase. **Weed Sci.** 1997;45:601-9.
- Macias F.A. et al. **Allelopathy - a natural alternative for weed control.** **Pest Manag Sci.** 2007;63:327-48.
- Macias F.A. et al. Evidence for an allelopathic interaction between rye and wild oats. **J Agric Food Chem.** 2014;62:9450-7.
- Mahidol C. et al. Mammea coumarins from the flowers of *Mammea siamensis*. **J Nat Prod.** 2002;65:757-60.
- Matos M.J. et al. Looking for new targets: simple coumarins as antibacterial agents. **Med Chem.** 2012;8:1140-5.

- Matos M.J. et al. Synthesis and structure-activity relationships of novel amino/nitro substituted 3-arylcoumarins as antibacterial agents. **Molecules**. 2013;18:1394-404.
- Morris M.P., Pagan C. Isolation of the toxic principles of mamey. **J Am Chem Soc**. 1953;75:1489.
- Morton J. Mamey. In: Morton J.F., editor. **Fruits of warm climates**. New Croplinks: 1987. p.304-7.
- Mukandiwa L. et al. Isolation of seselin from *Clausena anisata* (Rutaceae) leaves and its effects on the feeding and development of *Lucilia cuprina* larvae may explain its use in ethnoveterinary medicine. **J Ethnopharm**. 2013;150:886-91.
- Mungkornasawakul P. Pesticidal plant extract for reducing the agricultural use of harmful pesticides [thesis] Chiang Mai: Chiang Mai University, 2004.
- Murray R.D.H. Naturally occurring plant coumarins. In: **Progress in the chemistry of organic natural products**. Springer: New York, 1997. p.2-105.
- Nakajima S., Kawazu K. Coumarin and eupoinin, two inhibitors of insect development from leaves of *Eupatorium japonicum*. **Agric Biol Chem**. 1980;44:2893-9.
- Nicholson R.A. Excitatory actions of dehydroabietic acid on mammalian synaptosomes. **Pharmacol Toxicol**. 1994;75:274-9.
- Nuria C. et al. Operation allelopathy: An experiment investigating an alternative to synthetic agrochemicals. **J Chem Educ**. 2014;91:570-4.
- Olson M.M., Roseland C.R. Induction of the coumarins scopoletin and ayapin in sunflower by insect-feeding stress and effects of coumarins on the feeding of sunflower beetle (Coleoptera: Chrysomelidae). **Environ Entomol**. 1991;20:1166-72.
- Pereira A.M.S. et al. Influence of fertilizer on coumarin content and biomass production in *Mikania glomerata* Sprengel. **J Herb Spi Med Plant**. 1998;29-48.
- Prasad S.M., Prasad N., Barnwal M.K. Evaluation of insecticides against aphid vectors of virus diseases of French Bean. **J Plant Protect Environ**. 2006;3:87-90.
- Prats E. et al. Constitutive coumarin accumulation on sunflower leaf surface prevents rust germ tube growth and appressorium differentiation. **Crop Sci**. 2007;47:1119-24.
- Promsiri S. et al. Evaluations of larvicidal activity of medicinal plant extracts to *Aedes aegypti* (Diptera: Culicidae) and other effects on a non target fish. **J Insect Sci**. 2006;3:179-88.
- Rahman A.U. **Studies in natural product chemistry**. Amsterdam: Elsevier, 2000. v.24. p.860-1.
- Ramakrishna A., Ravishankar G.A. Influence of abiotic stress signals on secondary metabolites in plants. **Plant Signal Behav**. 2011;6:1720-31.
- Rattan R.S. Mechanism of action of insecticidal secondary metabolites of plant origin. **Crop Prot**. 2010;29:913-20.
- Razavi S.M. Plant coumarins as allelopathic agents. **Int J Biol Chem**. 2011;5:86-90.
- Razavi S.M., Zarrini G. Bioactivity of aviprin and aviprin-3-O-glucoside, two linear furanocoumarins from Apiaceae. **Russ J Bioorg Chem**. 2010;36:359-62.
- Rials C. et al. Phytotoxicity of cardoon (*Cynara cardunculus*) allelochemicals on standard target species and weeds. **J Agric Food Chem**. 2014;62:6699-706.
- Ribeiro C.V., Kaplan M.A. Tendências evolutivas de famílias produtoras de cumarinas em *angiospermae*. **Quim Nova**. 2002; 25:533-8.
- Rietjens I.M. et al. Molecular mechanisms of toxicity of important food-borne phytotoxins. **Mol Nutr Food Res**. 2005;49:13158.
- Riveiro M.E. et al. Coumarins: old compounds with novel promising therapeutic perspectives. **Curr Med Chem**. 2010;17:1325-38.

- Scarabel L., Varotto S., Sattin M. A European biotype of *Amaranthus retroflexus* cross-resistant to ALS inhibitors and response to alternative herbicides. **Weed Res.** 2007;47:527-33.
- Schinkovitz A. et al. Ostruthin: An antimycobacterial coumarin from the roots of *Peucedanum ostruthium*. **Planta Med.** 2003;69:369-71.
- Sharma D.C., Badiyala A., Choudhary A. Bioefficacy and persistent toxicity of biopesticides and insecticides against potato tuber moth, *Phthorimaea operculella* Zell. on spring potato. **Pestic Res J.** 2006;18:43-6.
- Stevenson P. et al. Insect antifeedent furanocoumarins from *Tetradium daniellii*. **Phytochemistry.** 2003;63:42-6.
- Thuong P.T. et al. Antioxidant activities of coumarins from Korean medicinal plants and their structure-activity relationships. **Phytother Res.** 2010;24:101-6.
- Tripathi A.K. et al. Insect feeding deterrent and growth inhibitory activities of scopoletin isolated from *Artemisia annua* against *Spilarctia obliqua* (Lepidoptera: Noctuidae). **Insect Sci.** 2011;18:189-94.
- Urbain A., Marston A., Hostettmann K. Coumarins from *Peucedanum ostruthium* as inhibitors of acetylcholinesterase. **Pharm Biol.** 2005;43:647-50.
- Venugopala K.N., Rashmi V., Odhav B. Review on natural coumarin lead compounds for their pharmacological activity. **BioMed Res Int.** 2013;1-14.
- Vera N. et al. Insect feeding deterrent and growth inhibitory activities of scopoletin isolated from *Artemisia annua* against *Spilarctia obliqua* (Lepidoptera: Noctuidae). **Chem Biodivers.** 2006;3:21-6.
- Wang X.B. et al. Nematocidal coumarins from *Heracleum candicans* Wall. **Nat Prod Res.** 2008;22:666-71.
- Yoshikawa H., Taniguchi E., Maekawa K. Synthesis and biological activities of isocoumarins. **J Pest Sci.** 1979;4:457-62.
- Zheng L., Zhao T., Sun L. Research progress of the pharmacological action and pharmacokinetics of coumarins. **Shi Guo Guoy.** 2013;24: 714-7.