Aliphatic C_{17}-Polyacetylenes of the Falcarinol Type as Potential Health Promoting Compounds in Food Plants of the Apiaceae Family

Lars P. Christensen*

Institute of Chemical Engineering, Biotechnology and Environmental Technology, University of Southern Denmark, Niels Bohrs Allé 1, DK-5230 Odense M, Denmark

Received: August 20, 2010; Accepted: November 10, 2010; Revised: November 11, 2010

Abstract: Many epidemiological studies have provided evidence that a high intake of fruits and vegetables is associated with a reduced risk for the development of cancer and cardiovascular diseases. Fruits and vegetables are known to contain health promoting components such as vitamins, minerals, antioxidants and dietary fibers, however, it is unclear which of these are responsible for the health promoting properties of fruits and vegetables. Aliphatic C_{17}-polyacetylenes of the falcarinol type, which occur in common food plants of the Apiaceae family such as carrot, celeriac, parsnip and parsley, have demonstrated interesting bioactivities including antibacterial, antimycobacterial, and antifungal activity as well as anti-inflammatory, anti-platelet-aggregatory, neuritogenic and serotonergic effects. In addition, the cytotoxicity of falcarinol type polyacetylenes towards human cancer cells, bioavailability, and their potential anticancer effect *in vivo* indicates that these compounds may contribute to the health effects of certain vegetables and hence could be important nutraceuticals. The bioactivity of falcarinol type polyacetylenes occurring in food plants of the Apiaceae family, their possible mode of action and possible health promoting effects are discussed in this review as well as the effect of storage, processing and other factors that can influence the content of these compounds in root vegetables and products. Moreover, recent patents on bioactivity of falcarinol type polyacetylenes and inventions making use of this knowledge are presented and discussed.

Keywords: Polyacetylenes, falcarinol type, anti-inflammatory, anticancer, bioactivity, bioavailability, extraction, genotypes, processing, vegetables, Apiaceae.

INTRODUCTION

Many epidemiological studies show an inverse association of fruit and vegetable intake with the risk of important diseases such as cancer and cardiovascular diseases [1-8]. Furthermore, data from epidemiological studies show that the daily intake of fruits and vegetables should be around 400 g or even higher in order to have health beneficial effects [3, 9]. Fruits and vegetables are known to contain components with health promoting actions such as vitamins, minerals, antioxidants and dietary fibers and most of these compounds have been evaluated in intervention studies [10]. In general, health benefits from supplementation have been proved mainly for groups that had particular low intake of these compounds, for example due to malnutrition, while supplementation at high levels provides only minor additional improvements [10], and in some cases may even result in adverse effects, as in the case of antioxidants such as β-carotene [11]. While it is generally accepted that most people should eat more fruits and vegetables, rather than supplements, in order to get adequate amounts of relevant nutrients it is not known why this is in fact better. Therefore, as long as the compounds in fruits and vegetables that make the greatest difference for health have not been identified it is not possible to conclude whether some fruits and vegetables are healthier to eat than others and to what extent cultivars/species or cultivation methods are important. Furthermore, it is not possible to conclude to what extent raw plant foods are better or worse than cooked ones or if a storage method increases or decreases value for health. Therefore, it is not surprising that there exist some discrepancies between different epidemiological investigations on the health effects of fruits and vegetables as the results of these studies most likely depend on many factors including intake, processing and which type of fruits and vegetables that are consumed. For example, in a very recent epidemiological study only a weak inverse association between overall cancer risk and high intake of fruits and vegetables was found [12], which is not consistent with results from other epidemiological studies [1-4, 7]. Once the compounds important for the health promoting properties of fruits and vegetables have been identified as well as additive and synergistic effects between different health promoting compounds have been elucidated, it will be possible to optimize the health effects of plant foods and to give more accurate diet recommendations in particular for people with special needs or preferences.

The present information about the health beneficial properties of plant foods indicate that common constituents such as vitamins minerals, and antioxidants cannot alone explain this effect; hence other health promoting compounds

*Address correspondence to this author at the Institute of Chemical Engineering, Biotechnology and Environmental Technology, Faculty of Engineering, University of Southern Denmark, Niels Bohrs Allé 1, DK-5230 Odense M, Denmark; Tel: +45 6550 7361; Fax: +45 6550 7354;
E-mail: lpc@kbm.sdu.dk

1876-1429/11 $100.00+.00

with unknown effects and/or unknown mechanisms of action, of which some have until now been overlooked, needs to be explored in order to get a more precise picture of the health promoting properties of fruits and vegetables. A few compounds are already known or suspected to have health benefits by other, less understood mechanisms, than those of minerals and vitamins, such as anticancer effects of glucosinolates and their degradation products from Brassicas [13-15], and plant sterols (phytosterols) [16] as well as protection against cardiovascular disease by sulfoxides and/or flavonoids from Alliums [17]. Other examples of groups of natural products that may contribute to the health effects of vegetable foods are glycolipids [18, 19], sesquiterpene lactones [8], and polyacetylenes [8, 20-30], and especially the latter group has in recent years received attention as potential health promoting compounds [8, 20-23, 25, 27, 29].

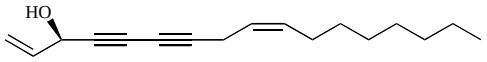
Polyacetylenes are widely distributed, occurring in plants, fungi, lichens, moss, marine algae and invertebrates [31-33]. More than 2000 polyacetylenes are known of which the majority have been isolated from higher plants and in particular from the botanically related plant families Apiaceae, Araliaceae, and Asteraceae [31, 33]. The triple bond functionality of polyacetylenes transforms these natural products to a very interesting group of compounds whose reactivity towards proteins and other biomolecules may explain their wide variety of bioactivities. Among the most interesting bioactivities of polyacetylenes from higher plants is their potential anticancer and anti-inflammatory activity as well as their activity against fungi and bacteria, which occurs at concentrations nontoxic for humans [23, 29, 33]. In particular, falcarinol (**1**) and related aliphatic C_{17}-polyacetylenes of the falcarinol type (Fig. (**1**)), present in, for example, many food and medicinal plants of the Apiaceae family possess interesting bioactivities. This type of polyacetylenes is highly cytotoxic and has a potential anticancer effect as demonstrated *in vitro* and *in vivo* [8, 20-24, 27, 29]. In addition, falcarinol type polyacetylenes also possess anti-inflammatory, anti-platelet-aggregatory, antibacterial, anti-mycobacterial, antifungal, neuritogenic, and immune stimulatory effects *in vitro* [8, 23, 25, 28, 29]. Consequently, polyacetylenes of the falcarinol type could turn out to be an important group of nutraceuticals that may contribute significantly to the health effects of certain vegetable foods and medicinal plants. Hence, if investigations in the future show that these compounds in fact exert positive health effects in human beings they are obvious targets for the development of healthier foods and food products as well as pharmaceuticals.

This review focuses on the bioactivity of polyacetylenes of the falcarinol type and their distribution in the edible parts of food plants of the Apiaceae family (former Umbelliferae). The effect of storage, processing and other factors such as genotypes and cultivation on the content of polyacetylenes is also described. Based on these findings, the role of polyacetylenes as potential health promoting compounds in food plants is discussed as well as their use as pharmaceuticals. In addition, this review cites recent and former patents focusing on extraction and isolation of polyacetylenes of the falcarinol type from plant material for the use in functional foods, dietary supplements, and medicinal preparations for the treatment and prevention of diseases.

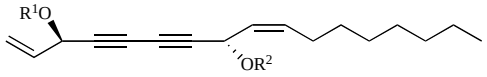
FALCARINOL TYPE POLYACETYLENES IN FOOD PLANTS OF THE APIACEAE FAMILY

Aliphatic C_{17}-polyacetylenes of the falcarinol type (Fig. (**1**)), are widespread amongst Apiaceae and Araliaceae plant species, and consequently almost all polyacetylenes found in the edible parts of food plants of the Apiaceae family are of the falcarinol type (Table **1**) [34-69]. Falcarinol type polyacetylenes are, however, less common in food plants of other plant families, although falcarinol (**1**) and falcarindiol (**2**) have been detected in tomatoes and aubergines of the Solanaceae, where they appear to be phytoalexins [70-72]. The structures of most polyacetylenes indicate that they are biosynthesized from unsaturated fatty acids. Feeding experiments with ^{14}C- and ^{3}H-labelled precursors have confirmed this assumption and further that polyacetylenes are build up from acetate and malonate units [31-33, 73-76]. The biosynthesis of polyacetylenes of the falcarinol type seems to follow the normal biosynthetic pathway for aliphatic C_{17}-polyacetylenes, with dehydrogenation of oleic acid to give a C_{18}-ditriyne acid intermediate, which is then transformed to C_{17}-diyne polyacetylenes by β-oxidation followed by the loss of CO_2 and H_2O. Further oxidation and dehydrogenation lead to polyacetylenes of the falcarinol type [29, 31, 33, 73].

Most polyacetylenes are thermally unstable and furthermore may undergo photodecomposition if exposed to ultraviolet (UV) light as well as oxidative and pH-dependent decomposition. This often provides substantial challenges for the isolation, quantification and characterization of these secondary metabolites [23, 30, 31, 33, 77]. Falcarinol type polyacetylenes have very characteristic UV-spectra due to their conjugated triple bonds and hence they are easily identified in extracts by UV detection [23, 31, 77-79]. In many cases, falcarinol type polyacetylenes only have two conjugated unsaturated bonds in their structure (Fig. (**1**)), and therefore the extinction coefficients (ε) of these compounds at their characteristic UV-maxima are low ($\varepsilon <$ 6000 for two triple bonds in conjugation) [23, 31, 78, 79]. Consequently, detection at 205 nm is preferred for falcarinol type polyacetylenes, although their characteristic UV-maxima occurs above 225 nm. Detection at 205 nm may improve the UV sensitivity of these compounds with a factor of 10 [23, 45]. This is important as many falcarinol type polyacetylenes in Apiaceae food plants often occur in relative low concentrations (down to 0.5 mg/kg fresh weight) [22, 23, 44-46, 48]. Qualitative and quantitative analyses of falcarinol type polyacetylenes in extracts have mainly been performed by high-performance liquid chromatography (HPLC) combined with photodiode array (PDA) or simple UV detection [20, 22, 23, 25, 28, 44-50, 68], although liquid chromatography-mass spectrometry (LC-MS) [22, 23, 50, 51] and capillary gas chromatographic (GC-FID and/or GC-MS) techniques [23, 52, 53, 69] are also described in the literature as suitable methods for analyzing these compounds. Several methods have been developed for extraction of polyacetylenes from Apiaceae food plants [23, 33]. The most used method is a multiple extraction (2-3 times) with ethyl acetate under stirring at room temperature in the dark at various time intervals with the samples being exposed to ultrasound before stirring resulting in an almost complete extraction of these compounds from the plant material [45, 46, 50]. For HPLC analysis of falcarinol type polyacetylenes,



1 Falcarinol (panaxynol)



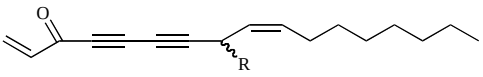
2 $R^1 = R^2 = H$, Falcarindiol

3 $R^1 = COCH_3$, $R^2 = H$, Falcarindiol-3-acetate

4 $R^1 = H$, $R^2 = COCH_3$, Falcarindiol-8-acetate

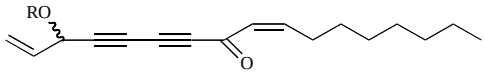
5 $R^1 = H$, $R^2 = CH_3$, Falcarindiol-8-methyl ether

6 $R^1 = R^2 = COCH_3$, Falcarindiol-3,8-diacetate



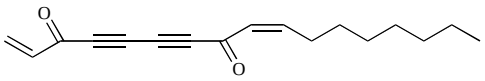
7 R = H, Falcarinone

8 R = OH, Falcarinolone

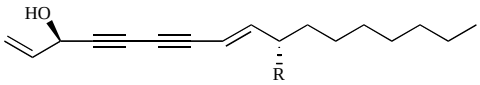


9 R = H, Isofalcarinone

10 R = $COCH_3$, 3-Acetoxy-falcarin-8-one

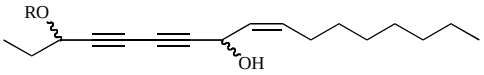


11 Falcarindione



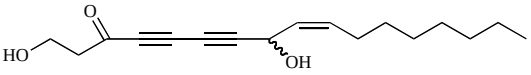
12 R = OH, Panaxydiol

13 R = OOH, Ginsenoyne K

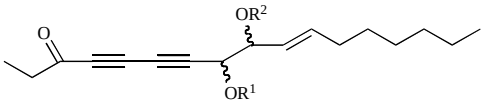


14 R = H, 1,2-Dihydrofalcarindiol

15 R = $COCH_3$,1,2-Dihydrofalcarindiol-3-acetate

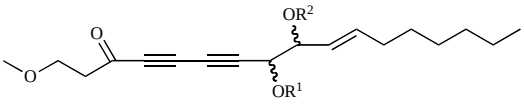


16 1-Hydroxy-1,2-dihydrofalcarinolone



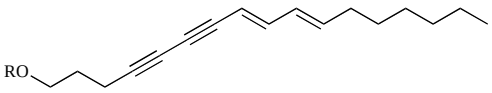
17 $R^1 = H$, $R^2 = COCH_3$, (*E*)-Falcarindiolone-9-acetate

18 $R^1 = COCH_3$, $R^2 = H$, (*E*)-Falcarindiolone-8-acetate



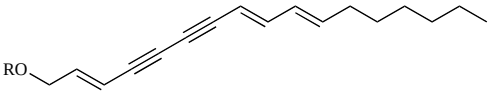
19 $R^1 = H$, $R^2 = COCH_3$, (*E*)-1-Methoxy-falcarindiolone-9-acetate

20 $R^1 = COCH_3$, $R^2 = H$, (*E*)-1-Methoxy-falcarindiolone-8-acetate



21 R = H, 2,3-Dihydrooenanthetol

22 R = $COCH_3$, 2,3-Dihydrooenanthetol acetate



23 R = H, Oenanthetol

24 R = $COCH_3$, Oenanthetol acetate

Fig. (1). Aliphatic C_{17}-polyacetylenes isolated from the edible parts of Apiaceae food plants.

a C_{18} reversed phase column is most often used in combination with a simple stepwise gradient consisting of aqueous acetonitrile containing increasing proportions of acetonitrile as the mobile phase [22, 23, 45, 46, 50].

BIOACTIVITY OF FALCARINOL TYPE POLYACETYLENES

Many plants of the Apiaceae and Araliaceae cause allergic contact dermatitis primarily due to occupational exposure [80, 81]. It has been demonstrated that falcarinol (**1**) is a potent contact allergen being responsible for many allergic skin reactions caused by plants of the above mentioned plant families [80-84]. However, allergic contact dermatitis from common vegetables of the Apiaceae is rare [85, 86], which is probably due to the relatively low concentrations of falcarinol in food plants compared to ornamental and wild plant species and/or due to a desensitizing effect of oral intake [80]. On the other hand, polyacetylenes such as falcarindiol (**2**) and falcarinone (**7**) do not seem to be

Table 1. Falcarinol Type Polyacetylenes in the Edible Parts of Food Plants of the Apiaceae, their Primary Uses and Plant Part Utilized.

Food Plants		Plant Part Used for Foods[a]	Primary Use[b]	Polyacetylenes in Used Plant Parts	References
Aegopodium podagraria L.	Bishop's weed, ground elder	L, St	V	**1, 2, 16**	[31, 34-36]
Anethum graveolens L.	Dill	L, S	C, V	**1, 2, 24**	[31, 35]
Anthriscus cerefolium (L.) Hoffm.	Chervil, salad chervil, French parsley	L, S	C, V	**1, 2**	[23, 29, 35]
A. sylvestris Hoffm.	Cow parsley	L	V	**2**	[23, 29, 37]
Apium graveolens L. var. *dulce*	Celery	L, S	C, V	**1, 2**	[29, 38]
A. graveolens L. var. *rapaceum*	Celeriac, knob celery, celery root	R	V	**1, 2, 5, 7, 8, 12**	[22, 31, 39]
Bunium bulbocastanum L.	Great earthnut	T, L, F	C, V	**1, 7, 8**	[31]
Carum carvi L.	Caraway	R, L, S	C	**1, 2, 8, 11**	[31, 35, 40]
Centella asiatica L.	Asiatic or Indian pennywort	L	V	**1, 2**	[29, 37]
Chaerophyllum bulbosum L.	Turnip-rooted chervil	R, L	V	**1, 7**	[23, 29]
Coriandrum sativum L.	Coriander, cilantro	L, S	C, V	**1, 2**	[29, 37]
Crithmum maritimum L.	Samphire, marine fennel	L	V	**1, 2**	[41, 42]
Cryptotaenia canadensis (L.) DC.	Hornwort, white or wild chervil	R, L, St, F	V	**1, 2**	[43]
Daucus carota L.	Carrot	R, L	V	**1-4, 6, 8-10, 12-15, 17-20**	[20-25, 27-29, 44-64]
Ferula assa-foetida L.	Asafoetida, giant fennel	R, S, Sh	C	**8**	[31]
F. communis L.	Common giant fennel	L, S	C, V	**2**	[65]
Foeniculum vulgare Mill.	Fennel	L, S	C, V	**1, 2**	[22, 35, 37]
Heracleum sphondylium L.	Common cow parsnip, hogweed	L, Sh	V	**1, 2**	[29, 35]
Levisticum officinale Koch.	Lovage, garden lovage	L, S	C, V	**1, 2, 8**	[23, 29, 66]
Oenanthe javanica (Blume) DC.	Water dropwort, water celery	L, St, Sh	V	**1, 2**	[23, 29, 67]
Pastinaca sativa L.	Parsnip	R, L	V	**1, 2, 7, 8**	[22, 31, 35, 68]
Petroselinum crispum (Mill.) Nyman ex A. W Hill.	Parsley	L	C, V	**1, 2, 7, 8**	[23, 29, 31, 35]
P. crispum (Mill.) Nyman ex A.W. Hill. var. *tuberosum*	Hamburg parsley, turnip-rooted parsley	R, L	C, V	**1, 2, 5, 12**	[22, 69]
Pimpinella major (L.) Hud.	Greater burnet saxifrage	R, L, S	C	**1, 2**	[23, 29, 35]
Sium sisarum L.	Skirret, chervil	R	V	**7**	[31, 40]
Trachyspermum ammi (L.) Spr.	Ajowan, ajwain	L, S	C	**21-24**	[31]

[a]R, roots; T, tubers; L, leaves; St, stems; Sh, shoots; F, flowers; S, seeds. [b]V, vegetable; C, condiment or flavouring [23, 29].

allergenic [82]. The allergenic properties of falcarinol indicate that it is very reactive towards thiol and/or amino groups in proteins, thus capable of forming hapten-protein complexes (antigens) [80-82]. The reactivity of falcarinol towards proteins is probably due to its hydrophobicity and its ability to form an extremely stable carbocation (resonance stabilized) with the loss of water, thereby acting as a very strong alkylating agent towards various biomolecules [21, 27, 29]. Although, no protein targets for falcarinol have so far been identified it has recently been demonstrated that falcarinol covalently binds to the cannabinoid CB_1 receptor and induces pro-allergic effects in skin thus confirming the alkylating properties of falcarinol [30]. The ability of falcarinol to bind covalently to various biomolecules may also be the case for related aliphatic C_{17}-polyacetylenes and hence may explain their cytotoxic, anti-inflammatory, anti-platelet-aggregatory, and antimicrobial effects *in vitro* as well as their potential anticancer activity as described in the following sections.

Antimicrobial Activity

Falcarinol (**1**) and falcarindiol (**2**) are important antifungal compounds. They have been shown to inhibit spore germination of various fungi in concentrations ranging from 20-200 μg/mL [23, 34, 54-57, 69-73, 87, 88]. Recent *in vitro* studies have also shown that falcarinol, falcarindiol and related C_{17}-polyacetylenes have antibacterial and antimycobacterial effects [41, 66, 89-91]. Especially the antimycobacterial effects towards *Mycobacterium* sp. [66, 91], and antibacterial effects towards resistant strains of the Gram-positive bacteria *Staphylococcus aureus* [89-91] are interesting. The anti-staphylococcal activity and effects against mycoplasma as well as other antibacterial effects occurred at approximately 10μg/mL, i.e., at nontoxic concentrations for humans, and thus represent pharmacological useful properties [89-91]. This indicates that falcarinol type polyacetylenes could have positive effects on human health, and may be used to develop new antibiotics if their antibacterial and antimycobacterial effects are confirmed *in vivo*.

Neurotoxic, Neuritogenic and Serotonergic Effects

Cicutoxin and oenanthotoxin (Fig. (**2**)), are aliphatic C_{17}-polyacetylenes, which occur in Apiaceae species such as water hemlock (*Cicuta virosa* L.) and hemlock water-dropwort (*Oenanthe crocata* L.). These compounds act directly on the central nervous system, causing convulsions and respiratory paralysis and hence are extremely poisonous [78, 92, 93]. The mode of action of cicutoxin and oenanthotoxin is probably related to their ability to interact with the γ-aminobutyric acid type A ($GABA_A$) receptors by inhibiting the specific binding of GABA antagonists to GABA-gated chlorine channels of $GABA_A$ receptors as demonstrated in the rat brain [94]. Binding of these ion channels therefore seems to play an important role in the acute toxicity of cicutoxin and oenanthotoxin. Structure-activity relationship studies in rodents with cicutoxin and related derivatives have shown that the length of the π–bond conjugated system in these polyacetylenes and the geometry of the double bonds is critical for the toxicological effects. Moreover, a terminal hydroxyl group and an allylic alcohol separated a certain distance of approximately 14 carbon atoms appear to be essential for neurotoxicity [93, 94]. The fact that falcarindiol (**2**) with two hydroxyl groups at a distance of 6 carbon atoms and falcarinol (**1**) with only one hydroxyl group do not exert convulsive action *in vitro* [93] support these findings. However, the neurotoxicity of falcarinol has been demonstrated upon injection into mice (LD_{50} = 100 mg/kg) [95] whereas the acute effects of falcarindiol are less as demonstrated by i.p. injection in rats with an LD_{50} > 200 mg/kg [94]. The type of neurotoxic symptoms produced by falcarinol is similar to those of cicutoxin. Cicutoxin with an LD_{50} < 3 mg/kg in rats is, however, much more toxic than falcarinol [94]. Poisoning of mammals from voluntary ingestion of natural sources of falcarinol has not been reported and therefore intake of food plants containing falcarinol is considered to be safe. Dill and/or ajowan contain the aliphatic C_{17}-polyacetylenes **21-24** (Table **1** and Fig. (**1**)) [23, 31], which are closely related to cicutoxin and oenanthotoxin (Fig. (**2**)). However, as these polyacetylenes do not fulfill the requirements for neurotoxicity they are not expected to exert any neurotoxic effects.

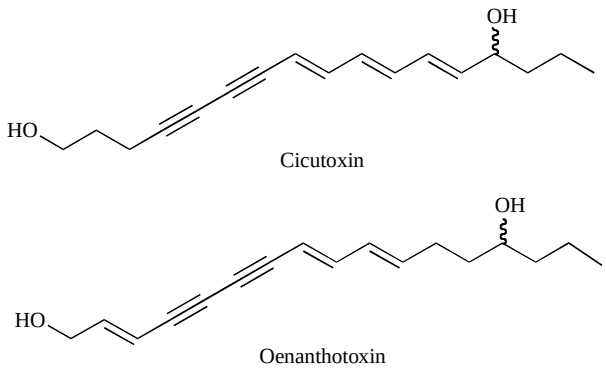


Fig. (2). Chemical structures of the neurotoxic aliphatic C_{17}-polyacetylenes cicutoxin and oenanthotoxin.

Falcarinol also seems to have an effect on neuritogenesis of cultured paraneurons. It has been demonstrated that falcarinol has a significant neuritogenic effect on paraneurons such as PC12 and Neuro2a cells at concentrations above 2μM [96, 97] and a neuroprotective effect on induced neuronal apoptosis [98]. Furthermore, it has been demonstrated that falcarinol improves scopolamine-induced memory deficit in mice. This effect is probably due to its ability to promote neuritogenesis of paraneurons [96]. If the neurito-genic and neuroprotective effect of falcarinol is confirmed in future *in vivo* studies, this polyacetylene may be considered as a candidate for the prevention and treatment of certain nervous system diseases such as Alzheimer's disease.

Falcarindiol has recently been isolated from the roots of *Angelica sinensis* (Oliv.) Diels (Apiaceae) by serotonin receptor ($5\text{-}HT_7$) binding assay-directed fractionation [99]. Thus falcarinol type polyacetylenes also seem to be serotonergic agents that may exhibit pharmacological effects related to the improvement of moods and behaviors.

Anti-Inflammatory and Anti-Platelet-Aggregatory Effects

The inflammatory process attracts leukocytes from the intravascular compartment to the site of damage, a process mediated by cytokines, chemokines, and cell surface proteins [100, 101]. Inflammation also leads to an induced expression of enzymes such as cyclooxygenases (COXs) and lipoxygenases (LOXs) that are involved in the synthesis of inflammatory mediators such as prostaglandin E_2. The transcription factor NF-κB plays a key role for the inducible expression of genes mediating pro-inflammatory effects and is thus an important target for the development of anti-inflammatory drugs. A large variety of inflammatory signals leads to an NF-κB activation, including lipopolysaccharide (LPS), nitric oxide (NO) and pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1β and TNF-α [25, 102]. In a recent study by Metzger *et al*. [25], it was demonstrated that extracts of purple carrots, containing very high concentrations of anthocyanins and other polyphenols, possess anti-

inflammatory activity by decreasing LPS induced production of IL-6, TNF-α and NO in macrophage cells in concentrations around 10μg/mL. Bioassay-guided fractionation of purple carrot extracts revealed that the anti-inflammatory activity was due to falcarinol (**1**), falcarindiol (**2**) and falcarindiol-3-acetate (**3**), which suggests that polyacetylenes are primarily responsible for the anti-inflammatory activity of carrots [25]. Falcarinol and falcarindiol are also strong inhibitors of LOXs (5-, 12- and 15-LOX) that are involved in tumor-progression and atherosclerosis processes [36, 103-106]. In addition, falcarindiol is an effective inhibitor of COXs, in particular COX-1. On the other hand the COX inhibitory activity of falcarinol does not seem to be pronounced [36, 103].

The anti-platelet-aggregatory effects of falcarinol and falcarindiol are probably related to their anti-inflammatory activity, and in particular their ability to inhibit certain LOXs that are responsible for the production of thromboxanes, e.g., thromboxane B_2 [65, 103, 107, 108]. In addition, it has been suggested that the anti-platelet-aggregatory activity of falcarinol is related to its ability to modulate prostaglandin catabolism by inhibiting the prostaglandin-catabolizing enzyme 15-hydroxy-prostaglandin dehydrogenase [109]. Falcarinol also has a significant anti-proliferative effect on vascular smooth muscle cells as demonstrated in rats at a concentration of 9μM [110]. Abnormal proliferation of vascular smooth muscle cells plays a central role in the pathogenesis of atherosclerosis [111]; hence falcarinol may have preventive effects on the development of this disease. The anti-inflammatory and anti-platelet-aggregatory activity of falcarinol type polyacetylenes may be explained by their alkylating properties being able to react with for example COXs, LOXs and NF-κB. Thus these polyacetylenes may have protective effects against development of cardiovascular diseases although these effects need to be validated by *in vivo* studies.

Cytotoxicity and Anticancer Effect

The potential anticancer activity of falcarinol type polyacetylenes was first discovered by the investigation of cytotoxic lipophilic root extracts of *Panax ginseng* C. A. Meyer (Araliaceae), which led to the isolation and identification of several cytotoxic falcarinol type polyacetylenes of which falcarinol, panaxydol and panaxytriol (Fig. (**1**)), (Fig. (**3**)), were found to be the most cytotoxic of the isolated polyacetylenes [23, 33, 87, 112-117]. Falcarinol (**1**), panaxydol and panaxytriol are highly cytotoxic to various cancer cell lines, such as leukemia (L-1210), human gastric adenocarcinoma (MK-1), mouse melanoma (B-16), and mouse fibroblast-derived tumor cells (L-929) [114-116]. The most toxic effect was observed for MK-1 cells with ED_{50} values of 0.027μg/mL, 0.016μg/mL, and 0.171μg/mL for falcarinol, panaxydol and panaxytriol, respectively [116]. In the same study these polyacetylenes were also shown to inhibit the growth of normal cell cultures such as human fibroblasts (MRC-5) with ED_{50} against normal cells being around 20 times higher compared to the tested cancer cells. This is in contrast to a recent study by Purup *et al.* [27], who investigated the differential effects of falcarinol and related C_{17}-polyacetylenes on human intestinal epithelial cells of cancer (Caco-2) and normal (FHs 74 Int.) origin, and found that the growth inhibitory effects on normal and cancer cells were almost the same for all investigated polyacetylenes. The selective *in vitro* cytotoxicity of falcarinol and related polyacetylenes against cancer cells compared to normal cells therefore appears to depend on the tested cell lines. Falcarindiol also possesses cytotoxic [22, 27, 42, 118, 119] and anti-mutagenic [120] activity *in vitro*, although it appears to be less bioactive than falcarinol. Falcarindiol-8-methyl ether (**5**) and panaxydiol (**12**) isolated from celeriac, parsley and carrots (Fig. (**1**) and Table **1**) are examples of further polyacetylenes from food plants exhibiting cytotoxic effect on human cancer and leukemia cell lines [22, 121].

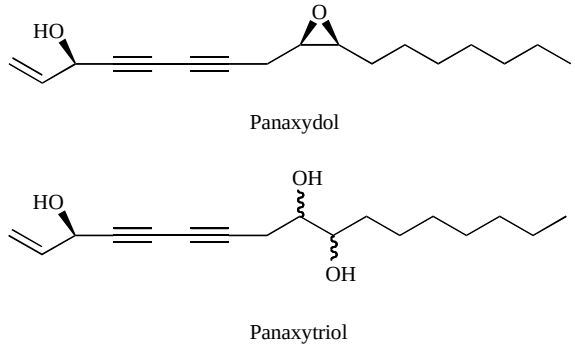


Fig. (3). Chemical structures of the cytotoxic polyacetylenes panaxydol and panaxytriol isolated from *Ginseng* species (Araliaceae).

The mechanisms for the cytotoxic activity and potential anticancer effect of falcarinol type polyacetylenes are not known but are most likely related to their alkylating properties and hence the presence of a hydroxyl group at C-3 as demonstrated in a recent study by Purup *et al.* [27] who studied the inhibitory effect of falcarinol and its oxidized form, falcarinone (**7**), on intestinal cell proliferation (Caco-2 and FHs 74 Int. cells). Purup *et al.* [27] showed that falcarinol significantly inhibited cell proliferation in Caco-2 cells at 2.5μg/mL ($P < 0.01$) and in FHs 74 Int. cells at 5 μg/mL ($P < 0.01$) whereas falcarinone only inhibited proliferation in Caco-2 cells at 20μg/mL ($P < 0.001$) and only tended to decrease proliferation in FHs 74 Int. cells at this concentration ($P < 0.10$). Furthermore, the dose of 20 μg/mL of falcarinone only caused 40-45% reduction in cell proliferation of both normal and cancer cells. These results demonstrate that falcarinone is a much less potent inhibitor of cell proliferation on intestinal cells of both normal and cancer origin and strongly support the hypothesis that the mode of action of falcarinol type polyacetylenes is due to their ability to lose water through the hydroxyl group at C-3, thereby generating reactive carbocations [21, 23, 27, 29]. This mode of action of falcarinol type polyacetylenes indicates that these compounds can affect the potential anticancer activity of each other in an antagonistic and/or synergistic manner. This hypothesis was also investigated by Purup *et al.* [27] who tested the inhibitory effect of falcarinol and falcarindiol on Caco-2 and FHs 74 Int. cells in different concentration ratios. Keeping one of the polyacetylenes constant at 1μg/mL, Caco-2 and FHs 74 Int. cells were incubated with falcarinol and falcarindiol in the ratios 1:1,

1:5, 1:10, 5:1 and 10:1. A synergistic response for the inhibitory effect of cell proliferation was observed by adding falcarindiol in 1, 5 and 10 times the concentration of falcarinol for both Caco-2 and FHs 74 Int. cells (Table **2**). By keeping falcarindiol constant, no synergistic response of cell proliferation was observed by adding falcarinol in 5 and 10 times the concentration of falcarindiol in neither Caco-2 nor FHs 74 Int. cells (Table **2**). These results demonstrate that falcarindiol in low doses can have very potent inhibitory effects on intestinal cell proliferation when found in combination with low doses of falcarinol. Synergistic interactions could therefore be an important factor in relation to the anticancer activity of falcarinol type polyacetylenes, although this activity clearly depends on the concentration and the ratio of the compounds. Furthermore, the results also demonstrate that the bioactivity of falcarinol type polyacetylenes including synergistic effects, are only expected from those compounds that are able to generate resonance stabilized carbocations.

The suppressive effect of falcarinol and falcarindiol on cell proliferation of tumor cells [122, 123] is probably related to the ability of these polyacetylenes to arrest the cell cycle progression of the cells at various phases of the cell cycles. This also indicates that falcarinol and falcarindiol are able to induce apoptosis as demonstrated in cancer cells *in vitro* [26, 123] and further support the hypothesis that the cytotoxic activity and potential anticancer effect of falcarinol type polyacetylenes are related to their reactivity towards nucleophiles and hence their ability to interact with various biomolecules.

Only a few studies have been conducted to investigate the anticancer effect of falcarinol type polyacetylenes *in vivo*. Preliminary *in vivo* evaluation of the cytotoxic activity of falcarinol type polyacetylenes using the LOX melanoma mouse xenocraft model demonstrated some potential for *in vivo* antitumor activity of these secondary metabolites including falcarinol and falcarindiol [118]. The most interes-ting findings on the potential anticancer effect of falcarinol type polyacetylenes are, however, from a preclinical study on rats demonstrating inhibitory effects of carrots and falcarinol on the development of colon cancer [21]. In the human diet, carrots are the major dietary source of falcarinol, although falcarinol may also be supplied by many other plant food sources (Table **1**). An *in vitro* study conducted by Hansen *et al*. [20] showed that falcarinol could stimulate differentiation of primary mammalian cells in concentrations between 0.001 and 0.1 μg/mL falcarinol. Toxic effects were found above > 0.5 μg/mL falcarinol, while the major carotenoid in carrots, β-carotene, had no effect at even 100 μg/mL [20]. This biphasic effect (hormesis) on cell proliferation has also recently been demonstrated for both falcarinol and falcarindiol on human intestinal epithelial cells (Caco-2 and FH 74 Int.) [26, 27] and is fully in accordance with the hypothesis that toxic compounds have beneficial effects at certain lower concentrations [124, 125]. Therefore, falcarinol and falcarindiol appear to be among the bioactive components in carrots, celeriac, parsley and related vegetables that could explain their preventive effects against cancer, rather than carotenoids, polyphenols or other natural products. This hypothesis is further supported by recent studies on the anti-inflammatory compounds of carrots [25] and bioavailability studies of falcarinol and falcarindiol in humans [23, 29]. For example, when falcarinol was administered orally via carrot juice (13.3 mg falcarinol/L carrot juice) in amounts of 900 mL, it was rapidly absorbed, reaching a maximum concentration in serum of 0.0023 μg/mL and 0.0020 μg/mL at 2 and 5 hours, respectively, after administration [23, 29]. This is within the range where the *in vitro* data indicate a potentially beneficial physiological effect, and a possible inhibitive effect on the proliferation of cancer cells [20, 23, 29].

Table 2. Effects of Different Ratios of Falcarinol and Falcarindiol on Caco-2 and FHs 74 Int. Cells in Culture Medium Containing 0.625% Fetal Calf Serum [27].[a]

		Falcarinol (μg/mL)			
		0	1	5	10
Falcarindiol (μg/mL)		**Caco-2 cells**			
	0	1.0	1.01 ± 0.25	0.36 ± 0.25	0.18 ± 0.01
	1	1.35 ± 0.36	0.71 ± 0.08[b]	0.58 ± 0.04	0.22 ± 0.08
	5	1.03 ± 0.32	0.53 ± 0.06[b]	ND[c]	ND
	10	0.52 ± 0.17	0.17 ± 0.03[b]	ND	ND
Falcarindiol (μg/mL)		**FHs 74 Int. cells**			
	0	1.0	1.02 ± 0.06	0.32 ± 0.35	0.06 ± 0.01
	1	0.92 ± 0.01	0.51 ± 0.30[b]	0.47 ± 0.01	0.36 ± 0.28
	5	0.90 ± 0.04	0.34 ± 0.24[b]	ND	ND
	10	0.60 ± 0.14	0.14 ± 0.13[b]	ND	ND

[a]Mean ± standard deviation is shown for each combination of falcarinol and falcarindiol. Data are presented relative to cell proliferation obtained in medium without polyacetylenes for two individual experiments. [b]Significant synergistic inhibitory effect on cell proliferation compared to single-compound assay ($P < 0.01$). [c]ND = not determined

The possible anticancer effect of falcarinol and carrots *in vivo* has been demonstrated in an established rat model for colon cancer as mentioned above. The rats were induced with colon cancer by injections of the carcinogen azoxymethane (AOM) followed by feeding with carrot or purified falcarinol [21]. Dietary treatments with carrot and falcarinol showed a significant (P = 0.028) tendency to reduce numbers of (pre)cancerous lesions with increasing size of lesion from no difference related to the control of the smallest lesions to a one-third reduction for the fully developed tumors. This indicates that dietary treatments with carrot and falcarinol were able to retard or delay the development of tumors in the rat model [21]. Although other major polyacetylene constituents in carrots such as falcarindiol and falcarindiol-3-acetate (**3**) probably have a similar mode of action as falcarinol, they probably have less bioactivity *in vivo* than falcarinol. The possibility to generate two active centers for nucleophilic attack in falcarindiol and falcarindiol-3-acetate reduces the lipophilic character of these compounds and hence their reactivity, in accordance with the observed non-allergenic properties of falcarindiol [82] and the less cytotoxic activity observed for falcarindiol compared to falcarinol. Although the direct effects of falcarindiol and falcarindiol-3-acetate are expected to be qualitatively similar but quantitatively less than those of falcarinol, they may be important bioactive constituents in carrots due to synergistic effects thereby affecting the anticancer activity of falcarinol significantly.

The present results clearly suggest that the protective effect of carrot against cancer can be explained to a high degree by its content of falcarinol and related aliphatic C_{17}-polyacetylenes, and not carotenoids or polyphenols as previously has been suggested [11, 126-129]. The cytotoxic activity of polyacetylenes of the falcarinol type towards cancer cells and possible *in vivo* anticancer effect indicates that these secondary metabolites may be valuable in the treatment and/or prevention of different types of cancer, and could contribute to the health promoting properties of certain food plants of the Apiaceae family.

EFFECT OF STORAGE, PROCESSING AND OTHER FACTORS ON THE CONTENT OF FALCARINOL TYPE POLYACETYLENES IN ROOT VEGETABLES

Falcarinol type polyacetylenes are unstable bioactive compounds being sensitive to heat and UV light that besides being potential nutraceuticals also play an important role in plant defence. Furthermore, some polyacetylenes of the falcarinol type, in particular falcarindiol contribute to the bitterness of some vegetables [46-48, 52, 53]. Consequently, the concentrations of falcarinol type polyacetylenes in food plants are important and it has been shown that the concentration of these polyacetylenes depends on factors such as genotype, storage, processing and cultivation [20, 44-46, 49, 50, 58, 68].

Genotypes and Cultivation

Kidmose *et al.* [44] demonstrated that the content of falcarinol (**1**), falcarindiol (**2**) and falcaridiol-3-acetate (**3**) varied significantly between 4 to 16 mg/kg fresh weight (FW), 19 to 54 mg/kg FW, and 9 to 19 mg/kg FW, respectively, in 6 genotypes of organically grown carrots, which is also in accordance with other studies on polyacetylenes in carrot genotypes [20, 45, 46]. Furthermore, it appears that the location where carrots are grown also has a significant impact on their content of polyacetylenes (Table **3**), whereas the growth system does not seem to have any significant effect on the content of falcarinol type polyacetylenes in carrots [50].

Thermal Processing

Carrots and other Apiaceae root vegetables are most often stored and processed before they reach the consumers. Thermal processing is a widely used method to inactivate enzymes before frozen storage or as part of cooking meals and it has been shown that thermal processing methods not surprisingly have a huge impact on the content of heat labile polyacetylenes in carrots and other root vegetables. For example, it has been demonstrated that steam blanching of carrot cubes or shreds at 90^{o}C for 2min can result in losses between 25-50% of major polyacetylenes (compounds **1**-**3**), which is in accordance with the 25% loss of falcarinol and falcarindiol observed in parsnip disks after blanching (90s, 95^{o}C) [68]. Boiling may even reduce the content further as demonstrated by Hansen *et al.* [20] who found a reduction of almost 70% in the content of falcarinol in carrot pieces boiled in water for 12 min compared to raw carrots. The reduction in the content of falcarinol and falcarindiol during boiling of carrots and parsnips is probably a combination of degradation of the polyacetylenes and conversion to related polyacetylenes such as falcarinone (**7**), falcarinolone (**8**) or falcarindione (**11**) during heating [68] and/or because the polyacetylenes are leached out into the water [20]. This is, however, not in fully accordance with the results of a recent study by Rawson *et al.* [49] who demonstrated that during water immersion thermal processing of carrots at high temperatures (70-90^{o}C) and long holding times (5-60min) the contents of polyacetylenes and in particular the content of falcarinol increased with increasing processing temperatures. Consequently, falcarinol according to this study is the most heat stable among the carrot polyacetylenes. The differences observed in the levels of polyacetylenes of thermal processed Apiaceae root vegetables are probably due to the fact that the quantitative analyses of polyacetylenes in some studies are based on dry weight basis as in the case of the study by Rawson *et al.* [49], whereas in other studies the quantitative measurements of polyacetylenes are performed on fresh weight basis [20, 44, 68]. The heat processing probably results in increased extractability of compounds as heat induces solubilization of the intercellular cementing pectin, thus, facilitating cell loosening [130]. In addition, a general increase in polyacetylene levels with longer holding times as observed by Rawson *et al.* [49] are probably attributed to the leaching of soluble solids from the root matrix [131] and retention of polyacetylenes, as these are largely insoluble in water. As a result, the proportion of dry weight polyacetylene levels appears to increase, which is not the case if the quantitative measurements were performed on fresh weight basis as the soluble solids to some extent would have been substituted by water. Although, further studies are needed to elucidate the impact on thermal processing of

Table 3. Content of Falcarinol, Falcarindiol and Falcarindiol-3-Acetate in Genotypes Grown at Two Locations [44]. Data are Means of Two Replications.

Genotype	Falcarinol (mg/kg FW[a])		Falcarindiol (mg/kg FW)		Falcarindiol-3-acetate (mg/kg FW)	
Location	**1**	**2**	**1**	**2**	**1**	**2**
Bolero	8.7	4.4	39.0	19.3	13.8	8.9
Duke	15.0	12.5	44.3	36.4	14.1	13.5
Express	6.0	7.3	30.4	29.1	10.9	11.0
Fancy	7.3	7.2	53.6	27.9	18.7	16.3
Line 1	15.5	10.3	49.4	25.1	12.2	8.5
Cortez	5.5	5.4	30.1	22.8	12.6	9.7
LSD[b]	3.1	2.0	12.7	5.1	4.4	4.3

[a]FW = fresh weight. [b]LSD = Least significant difference at $P \leq 0.05$.

Apiaceae root vegetables it is clear that thermal processing has a significant effect on the content and composition of falcarinol type polyacetylenes. Hence, development of methods for optimizing the thermal processing of these vegetables are important to improve their health promoting effects as well as to increase the acceptability of the products due to decreasing bitterness, since the levels of falcarindiol in processed samples will be too low to contribute to the sensory perception of bitterness. Finally, thermal processing may increase the bioavailability of falcarinol type polyacetylenes compared to raw root vegetables due the accessibility of these compounds and hence improve the health effects.

Storage

Storage is another important factor that may influence the content of polyacetylenes in Apiaceae root vegetables. It has been shown that the content of the major carrot polyacetylenes **1**-**3** is significantly higher in unprocessed whole carrots that were stored for 4 months at chilled temperatures (1°C) compared to frozen temperatures (-24°C) (Table **4**), indicating that there was a net production of polyacetylenes during postharvest storage or a smaller degradation of polyacetylenes than during frozen storage. Kjeldsen *et al.* [132] also reported that storage of carrots at 1°C for 4 months resulted in a significant increase in the total content of mono- and sesquiterpenes compared to frozen stored carrots indicating that the secondary metabolism in carrots at chilled temperatures is still active being able to produce secondary metabolites, including polyacetylenes. However, further investigations elucidating the metabolism of polyacetylenes in carrots during chilled storage are necessary to elucidate the metabolism of these compounds during storage. Finally, when the enzymes are inactivated by blanching the content of falcarinol type polyacetylenes appears to be stable during long term frozen storage (-24°C) as demonstrated for falcarinol in carrots [20]. Based on the present knowledge, storage has only a minor impact on the content of polyacetylenes compared to other factors such as genotype and processing, although it seems to be beneficial to store carrots and perhaps also related root vegetables at chilled temperatures until processing to improve the content of falcarinol type polyacetylenes and perhaps also other secondary metabolites.

RECENT INVENTIONS ON FALCARINOL TYPE POLYACETYLENES

A patent search revealed only a few recent patents or patent applications on aliphatic polyacetylenes of the falcarinol type related to the development of pharmaceuticals, functional foods and plant medicine with health-promoting effects for the prevention and treatment of various diseases.

The invention of Kenichi *et al.* [133] relates to the development of a pharmaceutical containing an active ingredient that inhibits calcium (Ca^{2+}) signal transduction and is to be used as a preventive and therapeutic agent against several diseases including allergy, cancer, dementia, type II diabetes, hypertension and angina. The active ingredient is a polyacetylenic compound such as falcarindiol (**2**) or dehydrofalcarindiol as well as other polyacetylenes of the falcarinol type contained in plants belonging to Apiaceae or Araliaceae plant families. Calcium plays a vital role in the physiology and biochemistry of organisms and the cell. For example it plays an important role in signal transduction pathways, where it acts as a second messenger, in neurotransmitter release from neurons, contraction of all muscle cell types, and enzymes require calcium ions as a cofactor such as in the blood-clotting cascade. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes. Consequently, an inhibition of calcium signal transduction may have an impact on the diseases mentioned in the patent [133].

Another invention by Gow *et al.* [134] relates to the use of compositions from the genus *Panax* (*Ginseng* species) comprising falcarinol type polyacetylenes, ginsenosides, and polysaccharides to be used to treat cardiovascular diseases, inflammatory diseases, neurodegenerative diseases, hepatitic disorders, viral diseases and cancer. The compositions of this invention are primarily intended to be used as oral delivery formulations in the forms of tablets, gel caps, or fast

Table 4. Content of Falcarinol, Falcarindiol and Falcarindiol-3-Acetate after 4 Month Storage at Chilled (1°C) and Frozen (-24°C) Temperatures [44]. Data are Means of Two Genotypes ('Bolero' and 'Line 1').

Polyacetylene	Chilled Storage	Frozen Storage	LSD[a]
Falcarinol (mg/kg FW[b])	16.2	11.0	4.2
Falcarindiol (mg/kg FW)	117.2	86.9	31.7
Falcarindiol-3-acetate (mg/kg FW)	25.5	17.1	6.4

[a]LSD = Least significant difference at $P \leq 0.05$. [b]FW = fresh weight.

dissolved tablets for use as dietary supplements or pharmaceutical compositions. This invention also describes methods comprising sequential solvent extraction and polymer absorbent purification to obtain fractions comprising the above mentioned bioactive constituents in order to obtain novel and more optimal profiles of bioactive compounds than those found in native plant material. The invention makes use of the present knowledge on the bioactivities of particular polyacetylenes and ginsenosides.

In an older invention by Nadler and Wen [135] a method of treating or inhibiting abnormal cardiac growth by using compounds that are able to inhibit the 12-lipoxygenase (12-LOX) pathway or action of the 12-LOX products, to reduce or eliminate 12-LOX pathway mediated cardiac hypertrophic effects at a cellular level is described. Among the active compounds mentioned in the invention with this inhibitive effect on the 12-LOX pathway is falcarinol (**1**) but also other falcarinol type polyacetylenes can be considered as active inhibitors of for example the 12-LOX pathway due to their anti-inflammatory effect being strong inhibitors of both LOXs and COXs (see section 'Anti-inflammatory and anti-platelet-aggregatory effects' of this review). An invention focusing on the anti-inflammatory activity of falcarinol type polyacetylenes is described in a Japanese patent filled by Yamahara [136]. In this invention the polyacetylenes falcarinol and falcarindiol contained in the medicinal plant *Angelica furcijuga* Kitagawa constitute a pharmaceutical composition with ant-inflammatory activity. Moreover, these polyacetylenes are according to the patent also useful as curing agents of diabetic peripheral neuropathy as they have excellent inhibiting action against aldose reduction enzymes of eye lenses and may also find use as anti-hepatitis agents as they inhibit rising of transaminase in serum. The compounds are obtained, for example, by extracting stems of *A. furcijuga* with methanol under reflux, concentrating the filtrate under reduced pressure to obtain a methanol extract and separating and purifying the methanol extract by various chromatographic techniques [136].

Although falcarinol type polyacetylenes are well known for their antimicrobial effects it is surprisingly that only a few patents on aliphatic polyacetylenes are related to this action. A recent invention by Dizer *et al.* [137] relates to the preparation of a Gram-negative bacteria biocide useful for inhibiting Gram-negative bacteria contaminating a medium. The biocide comprises one active ingredient obtainable by extraction of the outer sections of the root of Apiaceae vegetables, in particular the outer sections of carrot taproots. The invention further relate to natural food preservatives comprising the extract and methods producing the same. The active ingredient is not directly mentioned in the invention; however, the active component is likely to be falcarindiol, which is mainly present in the outer sections of carrots, whereas other polyacetylenes in carrots are mainly present in the inner sections of the carrot root [63]. Another recent invention by Graichen *et al.* [138] relates to a class of conjugated unsaturated compounds, to a method of preparing such compounds including their use as antimicrobial agents. The invention particularly relates to compounds containing three conjugated unsaturated moieties, of which two are at least acetylenic bonds. This invention, however, does not include falcarinol type polyacetylenes, although they have also demonstrated interesting antimicrobial activities (see section 'Antimicrobial activity' of this review). This invention clearly indicates that aliphatic polyacetylenes containing chromophores similar to those found in falcarinol type polyacetylenes are interesting antimicrobial compounds. In an older patent filed by Yoshimitsu and Takeshi [139], an extract of *Aralia cordota* Thunb. (Araliaceae) contains active components that can be used to treat viral diseases such as herpes. The active compounds include falcarindiol and dihydrofalcarindiol thus indicating that falcarinol type polyacetylenes also have anti-viral effects. The active components can be produced by extracting dried or callus-cultured *A. cordota* with, e.g., 75% ethanol for over 3 hours under refluxing, extracting the extract with water-containing ethyl acetate to obtain an ethyl acetate layer and water layer and subjecting the ethyl acetate to silica gel column chromatography using a mixture of chloroform and ethanol as eluents [139].

In a Japanese patent filed by Takeshi *et al.* [140], falcarinol contained in plant species of the Araliaceae and Apiaceae can be used for the prevention of carcinogenesis both as an ingredient in a drug or food. This is fully in accordance with the potential anticancer effect and cytotoxicity of falcarinol described in this review.

The last invention to be mentioned in this review is the one by Kim *et al.* [141], which relates to a composition for preventing harmful algae containing polyacetylenes such as falcarinol, falcarindiol as well as other aliphatic polyacetylenes. The composition prevents the harmful algae by selectively inhibiting the breeding of harmful algae such as blue-green algae or red tide. This invention demonstrates that falcarinol type polyacetylenes are a group of highly bioactive compounds that may find use for various applications of which some are not necessarily related to their health promoting effects.

In conclusion, current and former inventions use the bioactive properties of polyacetylenes of the falcarinol type

to produce products that can be used in the treatment or prevention of a long list of diseases including inflammatory diseases, antimicrobial effects, cancer, etc.

CURRENT & FUTURE DEVELOPMENTS

This review has demonstrated that aliphatic C_{17}-polyacetylenes of the falcarinol type comprise a group of natural products with important bioactivities such as antimycobacterial, antifungal, anti-inflammatory, anti-platelet-aggregatory, neuritogenic, serotonergic and anticancer activity. Although most of the demonstrated bioactivities of falcarinol type polyacetylenes are based on *in vitro* studies, these secondary metabolites should still be considered as possible important nutraceuticals that may contribute significantly to the health effects of food plants of the Apiaceae family. In addition, some polyacetylenes of the falcarinol type may be good candidates for developing new antibiotics and to prevent and treat cardiovascular diseases, cancer and certain nervous system diseases such as Alzheimer's disease. As it has been demonstrated that falcarinol type polyacetylenes are bioavailable the major challenge regarding to bioactive polyacetylenes is to confirm their possible health promoting effects *in vivo* in clinical as well as in further preclinical studies and to determine the optimal concentrations where health benefits are obtained. If this can be achieved the next step is to optimize the content of these compounds in foods by developing new genotypes and/or processing techniques.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGEMENTS

Financial support from the Danish Council for Strategic Research (Project No. 2101-01-0065) is gratefully acknowledged.

REFERENCES

[1] Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. Nutr Cancer 1992; 18(1): 1-29.

[2] Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: A review. J Am Diet Assoc 1996; 96(10): 1027-39.

[3] Van´t Veer P, Jansen MCJF, Klerk M, Kok FJ. Fruits and vegetables in the prevention of cancer and cardiovascular disease. Public Health Nutr 2000; 3(1): 103-7.

[4] Greenwald P, Clifford CK, Milner JA. Diet and cancer prevention. Eur J Cancer 2001; 37(8): 948-65.

[5] Kris-Etherton PM, Etherton TD, Carlson J, Gardner C. Recent discoveries in inclusive food-based approaches and dietary patterns for reduction in risk for cardiovascular disease. Curr Opin Lipid 2002; 13(4): 397-407.

[6] Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L, *et al.* Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am J Clin Nutr 2002; 76(1): 93-9.

[7] Maynard M, Gunnell D, Emmett P, Frankel S, Smith GD. Fruit, vegetables, and antioxidants in childhood and risk of adult cancer: The Boyd Orr cohort. J Epidemiol Commun Health 2003; 57(3): 218-25.

[8] Brandt K, Christensen LP, Hansen-Møller J, Hansen SL, Haraldsdóttir J, Jespersen L, *et al.* Health promoting compounds in vegetables and fruits: A systematic approach for identifying plant components with impact on human health. Trends Food Sci Technol 2004; 15(7-8): 384-93.

[9] Gundgaard J, Nielsen JN, Olsen J, Sørensen J. Increased intake of fruit and vegetables: Estimation of impact in terms of life expectancy and healthcare costs. Public Health Nutr 2003; 6(1): 25-30.

[10] Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, *et al.* Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: A postintervention follow-up in the SU.VI.MAX Study. Int J Cancer 2010; 127(8): 1875-81.

[11] Omenn GS, Goodmann GE, Thornquist MD, Balmes J, Cullen MR, Glass A, *et al.* Effects of a combination of *β*-carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996; 334(18): 1150-5.

[12] Boffetta P, Couto E, Wichmann J, Ferrari P, Trichopoulos D, Bueno-de-Mesquita HB, *et al.* Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2010; 102(8): 529-37.

[13] Lund E. Non-nutrive bioactive constituents of plants: Dietary sources and health benefits of glucosinolates. Int J Vit Nutr Res 2003; 73(2): 135-43.

[14] Thomalley PJ. Isothiocyanates: mechanism of cancer chemo-preventive action. Anticancer Drugs 2002; 13(4): 331-8.

[15] Kassie F, Uhl M, Rabot S, Grasl-Kraupp B, Verkerk R, Kundi M, *et al.* Chemoprevention of 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ)-induced colonic and hepatic preneoplastic lesions in the F344 rat by cruciferous vegetables administered simultaneously with the carcinogen. Carcinogenesis 2003; 24(2): 255-61.

[16] Awad AB, Fink CS. Phytosterols as anticancer dietary components: Evidence and mechanism of action. J Nutr 2000; 130(9): 2127-30.

[17] Griffiths G, Trueman L, Crowther T, Thomas B, Smith B. Onions-A global benefit to health. Phytother Res 2002; 16(7): 603-15.

[18] Larsen E, Christensen LP. Common vegetables and fruits a source of 1,2-di-*O*-*α*-linolenoyl-3-*O*-*β*-D-galactopyranosyl-*sn*-glycerol, a potential anti-inflammatory and antitumor agent. J Food Lipids 2007; 14(3): 272-9.

[19] Christensen LP. Galactolipids as potential health promoting compounds in vegetable foods. Recent Pat Food Nutr Agric 2009; 1(1): 50-8.

[20] Hansen SL, Purup S, Christensen LP. Bioactivity of falcarinol and the influence of processing and storage on its content in carrots (*Daucus carota* L.). J Sci Food Agric 2003; 83(10): 1010-7.

[21] Kobæk-Larsen M, Christensen LP, Vach W, Ritskes-Hoitinga J, Brandt K. Inhibitory effects of feeding with carrots or (-)-falcarinol on development of azoxymethane-Induced preneoplastic lesions in the rat colon. J Agric Food Chem 2005; 53(5): 1823-7.

[22] Zidorn C, Johrer K, Ganzera M, Schubert B, Sigmund EM, Mader J, *et al.* Polyacetylenes from the Apiaceae vegetables carrot, celery, fennel, parsley, and parsnip and their cytotoxic activities. J Agric Food Chem 2005; 53(7): 2518-23.

[23] Christensen LP, Brandt K. Bioactive polyacetylenes in food plants of the Apiaceae family: Occurrence, bioactivity and analysis. J Pharm Biomed Anal 2006; 41(3): 683-93.

[24] Young JF, Duthie SJ, Milne L, Christensen LP, Duthie GG, Bestwick CS. Biphasic effect of falcarinol on CaCo-2 cell proliferation, DNA damage, and apoptosis. J Agric Food Chem 2007; 55(3): 618-23.

[25] Metzger BT, Barnes DM, Reed JD. Purple carrot (*Daucus carota* L.) polyacetylenes decrease lipopolysaccharide-induced expression of inflammatory proteins in macrophage and endothelial cells. J Agric Food Chem 2008; 56(10): 3554-60.

[26] Young JF, Christensen LP, Theil PK, Oksbjerg N. The polyacetylenes falcarinol and falcarindiol affect stress responses in myotube cultures in a biphasic manner. Dose-Response 2008; 6(3): 239-51.

[27] Purup S, Larsen E, Christensen LP. Differential effects of falcarinol and related aliphatic C_{17}-polyacetylenes on intestinal cell proliferation. J Agric Food Chem 2009; 57(18): 8290-6.

[28] Metzger BT, Barnes DM. Polyacetylene diversity and bioactivity in orange market and locally grown colored carrots (*Daucus carota* L.). J Agric Food Chem 2009; 57(23): 11134-9.

[29] Christensen LP. Bioactivity of Polyacetylenes in Food Plants. In: Watson RR, Preedy VR, Eds. Bioactive Foods in Promoting Health. Oxford: Academic Press 2009; 285-306.

[30] Leonti M, Casu L, Raduner S, Cottiglia F, Floris C, Altmann K-H, *et al.* Falcarinol is a covalent cannabinoid CB_1 receptor antagonist and induces pro-allergic effects in skin. Biochem Pharmacol 2010; 79(12): 1815-26.

[31] Bohlmann F, Burkhardt T, Zdero C. Naturally Occurring Acetylenes. Academic Press: London 1973.

[32] Minto RE, Blacklock BJ. Biosynthesis and function of polyacetylenes and allied natural products. Prog Lipid Res 2008; 47(4): 233-306.

[33] Christensen LP, Jakobsen HB. Polyacetylenes: Distribution in Higher Plants, Pharmacological Effects and Analysis. In: Waksmundzka-Hajnos M, Sherma J, Kowalska T, Eds. Thin Layer Chromatography in Phytochemistry. Chromatographic Science Series. Boca Raton, FL: CRC Press/Taylor & Francis Group 2008; 99: 757-816.

[34] Kemp MS. Falcarindiol: An antifungal polyacetylene from *Aegopodium podagraria*. Phytochem 1978; 17(5): 1002.

[35] Degen T, Buser H-R, Städler E. Patterns of oviposition stimulants for carrot fly in leaves of various host plants. J Chem Ecol 1999; 25(1): 67-87.

[36] Prior RM, Lundgaard NH, Light ME, Stafford GI, van Staden J, Jäger AK. The polyacetylene falcarindiol with COX-1 activity isolated from *Aegopodium podagraria* L. J Ethnopharmacol 2007; 113(1): 176-8.

[37] Nakano Y, Matsunaga H, Saita T, Mori M, Katano M, Okabe H. Antiproliferative constituents in Umbelliferae plants II. Screening for polyacetylenes in some Umbelliferae plants, and isolation of panaxynol and falcarindiol from the root of *Heracleum moellendorffii*. Biol Pharm Bull 1998; 21(3): 257-61.

[38] Avalos J, Fontan GP, Rodriguez E. Simultaneous HPLC quantification of two dermatoxins, 5-methoxypsoralen and falcarinol, in healthy celery. J Liq Chromatogr 1995; 18(10): 2069-76.

[39] Bohlmann F. Polyacetylenforbindungen. 139. Notiz über die Inhaltsstoffe von Petersilie- und Sellerie-Wurzeln. Chem Ber 1967; 100(10): 3454-6.

[40] Bohlmann F, Arndt C, Bornowski H, Kleine K-M. Polyacetylenforbindungen. 31. Über Polyine aus der Familie der Umbelliferen. Chem Ber 1961; 94(4): 958-67.

[41] Meot-Duros L, Cerantola S, Talarmin H, Le Meur C, Le Floch G, Magne C. New antibacterial and cytotoxic activities of falcarindiol isolated in *Crithmum maritimum* L. leaf extract. Food Chem Toxicol 2010; 48(2): 553-7.

[42] Cunsolo F, Ruberto G, Amico V, Piattelli M. Bioactive metabolites from sicilian marine fennel. *Crithmum maritimum*. J Nat Prod 1993; 56(9): 1598-600.

[43] Eckenbach U, Lampman RL, Seigler DS, Ebinger J, Novak RJ. Mosquitocidal activity of acetylenic compounds from *Cryptotaenia canadensis*. J Chem Ecol 1999; 25(8): 1885-93.

[44] Kidmose U, Hansen SL, Christensen LP, Edelenbos M, Larsen E, Nørbæk R. Effects of genotype, root size, storage, and processing on bioactive compounds in organically grown carrots (*Daucus carota* L.). J Food Sci 2004; 69(9): S388-94.

[45] Christensen LP, Kreutzmann S. Determination of polyacetylenes in carrot roots (*Daucus carota* L.) by high-performance liquid chromatography coupled with diode array detection. J Sep Sci 2007; 30(4): 483-90.

[46] Kreutzmann S, Christensen LP, Edelenbos M. Investigation of bitterness in carrots (*Daucus carota* L.) based on quantitative chemical and sensory analyses. LWT-Food Sci Technol 2008; 41(2): 193-205.

[47] Schmiech L, Uemura D, Hofmann T. Reinvestigation of the bitter compounds in carrots (*Daucus carota* L.) by using a molecular sensory science approach. J Agric Food Chem 2008; 56(21): 10252-60.

[48] Schmiech L, Alayrac C, Witulski B, Hofmann T. Structure determination of bisacetylenic oxylipins in carrots (*Daucus carota* L.) and enantioselective synthesis of falcarindiol. J Agric Food Chem 2009; 57(22): 11030-40.

[49] Rawson A, Koidis, A, Patras A, Tuohy M, Brunton N. Modelling the effect of water immersion thermal processing on polyacetylene levels and instrumental colour of carrot disks. Food Chem 2010; 121(1): 62-8.

[50] Søltoft M, Eriksen MR, Trager AWB, Nielsen J, Laursen KH, Husted S, *et al.* Comparison of polyacetylene content in organically and conventionally grown carrots using a fast ultrasonic liquid extraction method. J Agric Food Chem 2010; 58(13): 7673-9.

[51] Pferschy-Wenzig E-M, Getzinger V, Kunert O, Woelkart K, Zahrl J, Bauer R. Determination of falcarinol in carrot (*Daucus carota* L.) genotypes using liquid chromatography/mass spectrometry. Food Chem 2009; 114(3): 1083-90.

[52] Czepa A, Hofmann T. Structural and sensory characterization of compounds contributing to the bitter off-taste of carrots (*Daucus carota* L.) and carrot puree. J Agric Food Chem 2003; 51(13): 3865-73.

[53] Czepa A, Hofmann T. Quantitative studies and sensory analyses on the influence of cultivar, spatial tissue distribution, and industrial processing on the bitter off-taste of carrots (*Daucus carota* L.) and carrot products. J Agric Food Chem 2004; 52(14): 4508-14.

[54] Garrod B, Lewis BG, Coxon DT. *Cis*-heptadeca-1,9-diene-4,6-diyne-3,8-diol, an antifungal polyacetylene from carrot root tissue. Physiol Plant Pathol 1978; 13(2): 241-6.

[55] Olsson K, Svensson R. The influence of polyacetylenes on the susceptibility of carrots to storage diseases. J Phytopathol 1996; 144(9-10): 441-7.

[56] Harding VK, Heale JB. Isolation and identification of the antifungal compounds accumulation in the induced resistance response of carrot slices to *Botrytis cinerea*. Physiol Plant Pathol 1980; 17(3): 277-89.

[57] Harding VK, Heale JB. The accumulation of inhibitory compounds in the induced resistance response of carrot root slices to *Botrytis cinerea*. Physiol Plant Pathol 1981; 18(1): 7-15.

[58] Lund ED, Bruemmer JH. Acetylenic compounds in stored packed carrots. J Sci Food Agric 1991; 54(2): 287-94.

[59] Bentley RK, Bhattacharjee D, Jones ERH, Thaller V. Natural acetylenes. Part XXVIII. C_{17}-Polyacetylenic alcohols from the Umbellifer *Daucus carota* L. (carrot): Alkylation of benzene by acetylenyl(vinyl)carbinols in the presence of toluene-*p*-sulphonic acid. J Chem Soc (C) 1969; (4): 685-8.

[60] Yates SG, England RE. Isolation and analysis of carrot constituents: myristicin, falcarinol, and falcarindiol. J Agric Food Chem 1982; 30(2): 317-20.

[61] Lund ED. Polyacetylenic carbonyl compounds in carrots. Phytochem 1992; 31(10): 3621-3.

[62] Lund ED, White JM. Polyacetylenes in normal and water-stressed 'Orlando Gold' carrots (*Daucus carota*). J Sci Food Agric 1990; 51(4): 507-16.

[63] Baranska M, Schulz H, Baranski R, Nothnagel T, Christensen LP. *in situ* Simultaneous analysis of polyacetylenes, carotenoids and polysaccharides in carrot roots. J Agric Food Chem 2005; 53(17): 6565-71.

[64] Yang R-L, Yan Z-H, Lu Y. Cytotoxic phenylpropanoids from carrot. J Agric Food Chem 2008; 56(9): 3024-7.

[65] Appendino G, Tagliapietra S, Nano GM. An anti-platelet acetylene from the leaves of *Ferula communis*. Fitoterapia 1993; 64(2): 179.

[66] Schinkovitz A, Stavri M, Gibbons S, Bucar F. Antimycobacterial polyacetylenes from *Levisticum officinale*. Phytother Res 2008; 22(5): 681-4.

[67] Fujita T, Kadoya Y, Aota H, Nakayama M. A new phenyl-propanoid glucoside and other constituents of *Oenanthe javanica*. Biosci Biotech Biochem 1995; 59(3): 526-8.

[68] Rawson A, Koidis A, Rai DK, Tuohy M, Brunton N. Influence of sous vide and water immersion processing on polyacetylene content and instrumental color of parsnip (*Pastinaca sativa*) disks. J Agric Food Chem 2010; 58(13): 7740-7.

[69] Nitz S, Spraul MH, Drawert F. C_{17} Polyacetylenic alcohols as the major constituents in roots of *Petroselinum crispum* Mill. ssp. *tuberosum*. J Agric Food Chem 1990; 38(7): 1445-7.

[70] De Wit PJGM, Kodde E. Induction of polyacetylenic phytoalexins in *Lycopersicon esculentum* after inoculation with *Cladosporium fulvum* (syn. *Fulvia fulva).* Physiol Plant Pathol 1981; 18(2): 143-8.

[71] Elgersma DM, Weijman ACM, Roeymans HJ, van Eijk GW. Occurrence of falcarinol and falcarindiol in tomato plants after infection with *Verticillium albo-atrum* and charcterization of four

phytoalexins by capillary gas chromatography-mass spectrometry. J Phytopathol 1984; 109(3): 237-40.

[72] Imoto S, Ohta Y. Elicitation of diacetylenic compounds in suspension cultured cells of eggplant. Plant Physiol 1988; 86(1): 176-81.

[73] Hansen L, Boll PM. Polyacetylenes in Araliaceae: Their chemistry, biosynthesis and biological significance. Phytochem 1986; 25(2): 285-93.

[74] Bu'Lock JD, Smalley HM. The biosynthesis of polyacetylenes. Part V. The role of malonate derivatives, and the common origin of fatty acids, polyacetylenes, and "acetate-derived" phenols. J Chem Soc 1962; 4662-4.

[75] Bu'Lock JD, Smith GN. The origin of naturally-occurring acetylenes. J Chem Soc (C) 1967; (5): 332-6.

[76] Barley GC, Jones ERH, Thaller V. Crepenynate as a Precursor of Falcarinol in Carrot Tissue Culture. In: Lam J, Breteler H, Arnason T, Hansen L, Eds. Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds (NOARC), Bioactive Molecules. Amsterdam: Elsevier 1988: 7: 85-91.

[77] Lam J, Hansen L. Polyacetylenes and Related Compounds: Analytical and Chemical Methods. In: Bowyer JR, Harwood J, Eds. Methods in Plant Biochemistry. London: Academic Press 1990; 4: 159-83.

[78] Wittstock U, Hadaček F, Wurz G, Teuscher E, Greger H. Polyacetylenes from water hemlock, *Cicuta virosa*. Planta Med 1995; 61(5): 439-45.

[79] Hadaček F, Werner A, Greger H. Computerized HPLC - diode array screening on characteristic acetylene patterns within *Peucedanum* (Umbelliferae - Apioideae). In: Lam J, Breteler H, Arnason T, Hansen L, Eds. Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds (NOARC), Bioactive Molecules. Amsterdam: Elsevier 1988: 7: 107-14.

[80] Hausen BM, Vieluf IK. Allergiepflanzen - Pflanzenallergene: Handbuch und Atlas der allergie-induzierenden Wild- und Kulturpflanzen. 2nd ed. Ecomed Verlagsgesellschaft mbH, Landsberg/München 2001.

[81] Paulsen E, Christensen LP, Andersen KE. Dermatitis from common ivy (*Hedera helix* L. subsp. *helix*) in Europe: past, present, and future. Contact Dermatitis 2010; 62(4): 201-9.

[82] Hansen L, Hammershøy O, Boll PM. Allergic contact dermatitis from falcarinol isolated from *Schefflera arboricola*. Contact Dermatitis 1986; 14(2): 91-3.

[83] Hausen BM, Bröhan J, König WA, Faasch H, Hahn H, Bruhn G. Allergic and irritant contact dermatitis from falcarinol and didehydrofalcarinol in common ivy (*Hedera helix* L.). Contact Dermatitis 1987; 17(1): 1-9.

[84] Oka K, Saito F, Yasuhara T, Sugimoto A. The allergens of *Dendropanax trifidus* Makino and *Fatsia japonica* Decne. et Planch. and evaluation of cross-reactions with other plants of the Araliaceae family. Contact Dermatitis 1999; 40(4): 209-13.

[85] Murdoch SR, Dempster J. Allergic contact dermatitis from carrot. Contact Dermatitis 2000; 42(4): 236.

[86] Machado S, Silva E, Massa A. Occupational allergic contact dermatitis from falcarinol. Contact Dermatitis 2002; 47(2): 113-4.

[87] Christensen LP. Biological activities of naturally occurring acetylenes and related compounds from higher plants. Recent Res Dev Phytochem 1998; 2(2): 227-57.

[88] Lutomski J, Luan TC, Hoa TT. Polyacetylenes in the Araliaceae family. Part IV. The antibacterial and antifungal activities of two main polyacetylenes from *Panax vietnamensis* Ha et Grushv. and *Polyscias fruticosa* (L.) Harms. Herb Polonica 1992; 38(2): 137-40.

[89] Chou S-C, Everngam MC, Sturtz G, Beck JJ. Antibacterial activity of components from *Lomatium californicum*. Phytother Res 2006; 20(2): 153-6.

[90] Lechner D, Stavri M, Oluwatuyi M, Pereda-Miranda R, Gibbons S. The anti-staphylococcal activity of *Angelica dahurica* (Bai Zhi). Phytochem 2004; 65(3): 331-5.

[91] Kobaisy M, Abramowski Z, Lermer L, Saxena G, Hancock REW, Towers GHN, *et al.* Antimycobacterial polyynes of Deveil's Club (*Oplopanax horridus*), a North American native medicinal plant. J Nat Prod 1997; 60(11): 1210-3.

[92] Starreveld E, Hope E. Cicutoxin poisoning. Neurology 1975; 25(8): 730-4.

[93] Wittstock U, Lichtnow KH, Teuscher E. Effects of cicutoxin and related polyacetylenes from *Cicuta virosa* on neuronal action potentials: A comparative study on the mechanism of the convulsive action. Planta Med 1997; 63(2): 120-4.

[94] Uwai K, Ohashi K, Takaya Y, Ohta T, Tadano T, Kisara K, *et al.* Exploring the structural basis of neurotoxicity in C_{17}-polyacetylenes isolated from water hemlock. J Med Chem 2000; 43(23): 4508-15.

[95] Crosby DG, Aharonson N. The structure of carotatoxin, a natural toxicant from carrot. Tetrahedron 1967; 23(1): 465-72.

[96] Yamazaki M, Hirakura K, Miyaichi Y, Imakura K, Kita M, Chiba K, *et al.* Effect of polyacetylenes on the neurite outgrowth of neuronal culture cells and scopolamine-induced memory impairment in mice. Biol Pharm Bull 2001; 24(12): 1434-6.

[97] Wang Z-J, Nie B-M, Chen H-Z, Lu Y. Panaxynol induces neurite outgrowth in PC12D cells *via c*AMP- and MAP kinase-dependent mechanisms. Chem Biol Interact 2006; 159(1): 58-64.

[98] Nie B-M, Jiang X-Y, Cai J-X, Fu S-L, Yang L-M, Lin L, *et al.* Panaxydol and panaxynol protect cultured cortical neurons against Aβ25–35-induced toxicity. Neuropharmacology 2008; 54(5): 845-53.

[99] Deng S, Chen S-N, Yao P, Nikolic D, van Breemen RB, Bolton JL, *et al.* Serotonergic activity-guided phytochemical investigation of the roots of *Angelica sinensis*. J Nat Prod 2006; 69(4): 536-41.

[100] Marra F. Chemokines in liver inflammation and fibrosis. Front Biosci 2002; 7: D1899-914.

[101] Schaerli P, Moser B. Chemokines: control of primary and memory T-cell traffic. Immunol Res 2005; 31(1): 57-74.

[102] Calzado MA, Lüdi KS, Fiebich B, Ben-Neriah Y, Bacher S, Munoz E, *et al.* Inhibition of NF-κB activation and expression of inflammatory mediators by polyacetylene spiroketals from *Plagius flosculosus*. Biochim Biophys Acta 2005; 1729(2): 88-93.

[103] Alanko J, Kurahashi Y, Yoshimoto T, Yamamoto S, Baba K. Panaxynol, a polyacetylene compound isolated from oriental medicines, inhibits mammalian lipoxygenases. Biochem Pharmacol 1994; 48(10): 1979-81.

[104] Liu J-H, Zschocke S, Bauer R. A polyacetylenic acetate and a coumarin from *Angelica pubescens* f. *biserrata*. Phytochem 1998; 49(1): 211-3.

[105] Schneider I, Bucar F. Lipoxygenase inhibitors from natural plant sources. Part 1. Medicinal plants with inhibitory activity on arachidonate 5-lipoxygenase and 5-lipoxygenase/cyclooxygenase. Phytother Res 2005; 19(2): 81-102.

[106] Schneider I, Bucar F. Lipoxygenase inhibitors from natural plant sources. Part 2. Medicinal plants with inhibitory activity on arachidonate 12-lipoxygenase, 15-lipoxygenase and leukotriene receptor antagonists. Phytother Res 2005; 19(4): 263-72.

[107] Kuo S-C, Teng C-M, Lee J-C, Ko F-N, Chen S-C, Wu T-S. Antiplatelet components in *Panax ginseng*. Planta Med 1990; 56(2): 164-7.

[108] Teng C-M, Kuo S-C, Ko F-N, Lee JC, Lee L-G, Chen S-C, *et al.* Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. Biochim Biophys Acta 1989; 990(3): 315-20.

[109] Fujimoto Y, Sakuma S, Komatsu S, Sato D, Nishida H, Xiao Y-Q, *et al.* Inhibition of 15-hydroxyprostaglandin dehydrogenase activity in rabbit gastric antral mucosa by panaxynol isolated from oriental medicines. J Pharm Pharmacol 1998; 50(9): 1075-8.

[110] Jiang L-P, Lu Y, Nie B-M, Chen H-Z. Antiproliferative effect of panaxynol on RASMCs *via* inhibition of ERK1/2 and CREB. Chem Biol Interact 2008; 171(3): 348-54.

[111] Ross R. Mechanisms of disease - Atherosclerosis - An inflammatory disease. N Engl J Med 1999; 340(2): 115-26.

[112] Shim SC, Koh HY, Han BH. Polyacetylene compounds from *Panax ginseng* C. A. Meyer. Bull Korean Chem Soc 1983; 4(4): 183-8.

[113] Fujimoto Y, Satoh M. A new cytotoxic chlorine-containing polyacetylene from the callus of *Panax ginseng*. Chem Pharm Bull 1988; 36(10): 4206-8.

[114] Ahn B-Z, Kim S-I. Relation between structure and cytotoxic activity of panaxydol analogs Analogen against L1210 cells. Arch Pharm 1988; 321(2): 61-3.

[115] Matsunaga H, Katano M, Yamamoto H, Mori M, Takata K. Studies on the panaxytriol of *Panax ginseng* C. A. Meyer. Isolation, determination and antitumor activity. Chem Pharm Bull 1989; 37(5): 1279-81.

[116] Matsunaga H, Katano M, Yamamoto H, Fujito H, Mori M, Takata K. Cytotoxic activity of polyacetylene compounds in *Panax ginseng* C. A. Meyer. Chem Pharm Bull 1990; 38(12): 3480-2.

[117] Siddiq A, Dembitsky V. Acetylenic anticancer agents. Anti-Cancer Agents Med Chem 2008; 8(2): 132-70.

[118] Bernart MW, Cardellina II JH, Balaschak MS, Alexander M, Shoemaker RH, Boyd MR. Cytotoxic falcarinol oxylipins from *Dendropanax arboreus*. J Nat Prod 1996; 59(8): 748-53.

[119] Fujioka T, Furumi K, Fujii H, Okabe H, Mihashi K, Nakano Y, *et al.* Antiproleferative constituents from Umbelliferae plants. V. A new furanocoumarin and falcarindiol furanocoumarin ethers from the root of *Angelica japonica*. Chem Pharm Bull 1999; 47(1): 96-100.

[120] Miyazawa M, Shimamura H, Bhuva RC, Nakamura S, Kameoka H. Antimutagenic activity of falcarindiol from *Peucedanum praeruptorum*. J Agric Food Chem 1996; 44(11): 3444-8.

[121] Ahn B-Z, Kim S-I. Heptadeca-1,8*t*-diene-4,6-diyne-3,10-diol, a further cytotoxic substance from Korean ginseng roots which is active against L1210 cells. Planta Med 1988; 54(2): 183.

[122] Kuo Y-C, Lin Y.L, Huang C-P, Shu J-W, Tsai W-J. A tumor cell growth inhibitor from *Saposhnikovae divaricata*. Cancer Invest 2002; 20(7-8): 955-64.

[123] Sun S, Du G-J, Qi L-W, Williams S, Wang C-Z, Yuan C-S. Hydrophobic constituents and their potential anticancer activities from Devil's Club (*Oplopanax horridus* Miq.). J Ethnopharmacol 2010; in press.

[124] Calabrese EJ, Baldwin LA. The hormetic dose-response model is more common than the threshold model in toxicology. Toxicol Sci 2003; 71(2): 246-50.

[125] Calabrese EJ. Hormesis: From marginalization to mainstream: A case for hormesis as the default dose-response model in risk assessment. Toxicol Appl Pharmacol 2004; 197(2): 125-36.

[126] Arscott SA, Tanumihardjo SA. Carrots of many colors provide basic nutrition and bioavailable phytochemicals acting as a functional food. Comp Rev Food Sci Food Saf 2010; 9(2): 223-39.

[127] Greenberg ER, Baron JA, Karagas MR, Stukel TA, Nierenberg DW, Stevens MM, *et al.* Mortality associated with low plasma concentration of β-carotene and the effect of oral supplementation. JAMA 1996; 275(9): 699-703.

[128] Michaud DS, Feskanich D, Rimm EB, Colditz GA, Speizer FE, Willett WC, *et al.* Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. Am J Clin Nutr 2000; 72(4): 990-7.

[129] Wright ME, Mayne ST, Swanson CA, Sinha R, Alavanja MCR. Dietary carotenoids, vegetables, and lung cancer risk in women: The Missouri Women's Health Study (United States). Cancer Causes Control 2003; 14(1): 85-96.

[130] Roeck AD, Sila DN, Duvetter T, Loey AV, Hendrickx M. Effect of high pressure/high temperature processing on cell wall pectic substances in relation to firmness of carrot tissue. Food Chem 2008; 107(3): 1225-35.

[131] Cazor A, Deborde C, Moing A, Rolin D, This H. Sucrose, glucose, and fructose extraction in aqueous carrot root extracts prepared at different temperatures by means of direct NMR measurements. J Agric Food Chem 2006; 54(13): 4681-6.

[132] Kjeldsen F, Christensen LP, Edelenbos M. Changes in volatile compounds of carrots (*Daucus carota* L.) during refrigerated and frozen storage. J Agric Food Chem 2003; 51(18): 5400-7.

[133] Kenichi, K., Hiroyuki, E., Kuniyoshi, M. Calcium^{2+} signal transduction inhibitor. JP2005000044775 (**2006**).

[134] Gow, R.T., Sypert, G.W., Li, D., Yan, X. Methods and compositions comprising *Panax* species. US20070065526 (**2007**).

[135] Nadler, J.L., Wen, Y. Method of treating or preventing abnormal cardiac cell growth by inhibiting the 12-lipoxygenase pathway. WO9959562 (**1999**).

[136] Yamahara, J. Pharmaceutical composition. JP1998000250896 (**1999**).

[137] Dizer, D., Alon, R., Kanner, Y. Gram negative biocide obtainable from Apiaceae vegetables. WO2009IB0007516 (**2010**).

[138] Graichen, F. H. M., Kyi, S., O'Shea, M. S., Warden, A. C. Conjugated unsaturated compounds. WO2009111830 (**2009**).

[139] Yoshimitsu, A., Takeshi, U. Agent for treatment of disease caused by virus such as herpes. JP1993000041667 (**1994**).

[140] Takeshi, M., Michihiro, S., Haruo, I., Harukuni, T., Akiko, M., Toshiya, S. Preventive of carcinogenesis. JP3287526 (**1991**).

[141] Seog, K.J., Sup, C.J., Cheol, K.J., Ki, M.S. Composition for control of harmful algae comprising polyacetylene compounds. KR2007100104641 (**2009**).