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Review

Chemistry and pharmacology of *Rhaponticum carthamoides*: A review

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ABSTRACT

Rhaponticum carthamoides (Willd.) Iljin is a perennial herb, commonly known as a maral root or Russian leuzea, which has been used for centuries in eastern parts of Russia for its marked medicinal properties. This review based on 117 literary sources, with many of them being originally published in non-English languages (mainly in Russian), discusses the current knowledge of traditional uses, chemistry, biological effects and toxicity of this species. Several different classes of compounds were previously isolated from various parts of *R. carthamoides* of which the main groups are steroids, particularly ecdysteroids, and phenolics (flavonoids and phenolic acids) accompanied with polyacetylenes, sesquiterpene lactones, triterpenoid glycosides and terpenes (essential oil). A comprehensive account of the chemical constituents is given in this review (figures of 120 structures are shown). Various types of preparations, extracts and individual compounds derived from this species have been found to possess a broad spectrum of pharmacological effects on several organs such as the brain, blood, cardiovascular and nervous systems as well as on different biochemical processes and physiological functions including proteosynthesis, work capacity, reproduction, and sexual function. Moreover, the extracts and preparations from the plant, which are hopefully safe, exhibited various additional biological effects e.g. antioxidant, immunomodulatory, anticancerogenic, antimicrobial, antiparasitic and insect antifeedant or repellent activities. The results of data analysis on the chemical, pharmacological and toxicological characteristics of *R. carthamoides* support the view that this species has beneficial therapeutic properties and indicate its potential as an effective adaptogenic herbal remedy. Finally, some suggestions for further research on chemical and pharmacological properties are given in this review.

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1. Introduction

Rhaponticum carthamoides (Willd.) Iljin (family Asteraceae), commonly known as a maral root or Russian leuzea, is a perennial herb, up to 150 cm high (Figs. 1 and 2), endemic in the Altai and Saian Mountains of South Siberia, where it naturally occurs in the alpine and subalpine meadows at 1200–2300 m above sea level (Selivanova, 1979; Lotocka and Geszprych, 2004). During the last few decades, the plant has been introduced to various regions of Central and Eastern Europe, where it is now widely grown for its marked medicinal properties (Opletal et al., 1997). The history of *R. carthamoides* as a medicinal plant began ages ago when local hunters in Altai observed the behaviour of the maral deer (*Cervus elaphus sibiricus*), which seemed to restore its strength after feeding on its roots. Their observation gave the traditional name "maral root" to the plant and initiated its use by local healers (Hlava and Valicek, 1989). In traditional medicine of Siberia, it has long been used in cases of overstrain and common weakness after illness (Petkov et al., 1984). In the last century, the muscle- and strength-building qualities of *R. carthamoides* have been thoroughly investigated in Russia, and various preparations have been commonly used by elite Soviet and Russian athletes in order to upgrade psychological and physical reserves which were exhausted by hard training (Gadzhieva et al., 1995). Currently, the extracts or some compounds from roots and rhizomes are used for their adaptogenic and tonic properties in various dietary supplements or nutraceutical preparations to promote muscle growth, treat impotency, eliminate physical weakness and mental weariness, as well as for recovery after surgery, infectious disease or chemical intoxication. They are also included in the formulas of various non-alcoholic beverages, cosmetic and bath products. Dried underground or aerial parts are included in herbal teas (Opletal and Opletalova, 1990; Opletal et al., 1997).

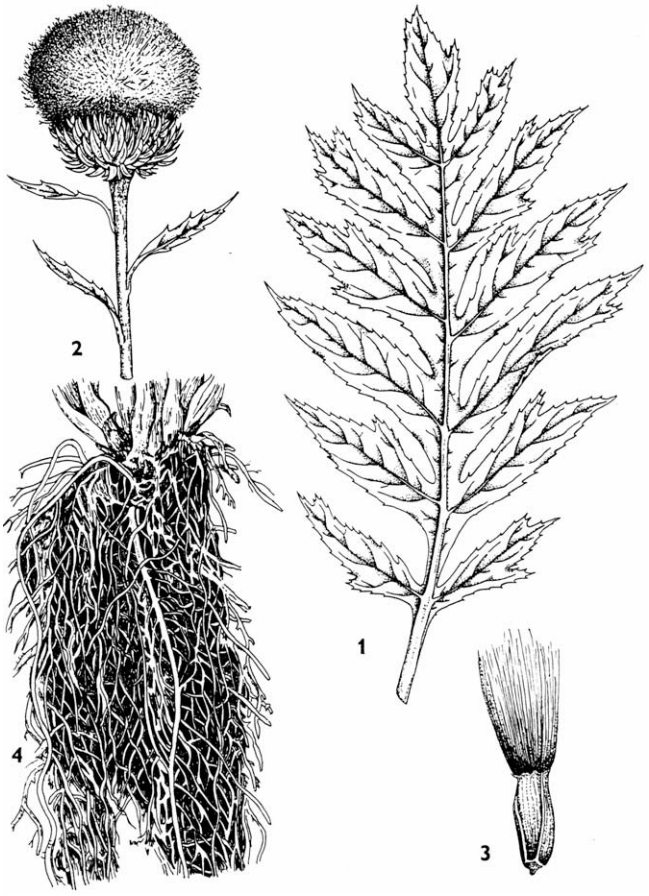


Fig. 1. Line drawing of *R. carthamoides*: 1. leaf, 2. inflorescence, 3. fruit, 4. roots (Valicek et al., 2001).

From a botanical point of view, it should be noted that the nomenclature of the genus is particularly confusing because many species of other genera are synonymous (Klein, 2004). Various species of the genera *Centaurea*, *Cnicus*, *Fornicium*, *Leuzea*, *Serratula*, and *Stemmacantha* are commonly listed in plant databases as synonyms for *R. carthamoides* (The International Plant Names Index, 2004). A particular question is whether to employ the name *Leuzea carthamoides* DC. or *R. carthamoides*. A recent treatment of the Cardueae tribe has chosen the latter (Greuter, 2003), suggesting that *L. carthamoides* be an additional synonym, which is, however, still widely used in many pharmacological and phytochemical studies. Nevertheless, despite many previous attempts to elucidate systematics of the genus (e.g. Dittrich, 1973; Holub, 1973, 1974; Soskov, 1978) including the latest one by Greuter (2003), the taxonomical status of the *R. carthamoides* appears to be still unclear and needs more detailed consideration.

2. Chemical composition

Several different classes of compounds were previously isolated from various parts of *R. carthamoides*, with the main groups being steroids, particularly ecdysteroids, and phenolics (Lamer-Zarawska et al., 1996; Opletal et al., 1997).

One of the earlier phytochemical reports regarding ecdysteroids of *R. carthamoides* revealed the isolation of 20-hydroxyecdysone (20E), known previously as β-ecdysone, ecdysterone or polypodine A (**1**), and inokosterone (**12**) from its underground parts (Krasnov et al., 1977). Further investigations identified 20E as the most abundant ecdysteroid in various parts of the plant with a content of 0.04–0.81%, 0.03–1.22% and 0.27–1.51% of dry matter for roots, aerial part and seeds, respectively (Yakubova and Sakharova, 1980; Varga et al., 1986; Opletal and Opletalova, 1990; Repcak et al., 1994; Timofeev et al., 1998). During more than 30 years of intensive research on the chemistry of *R. carthamoides*, 50 various ecdysteroid compounds (Table 1) have been detected in roots, aerial parts or seeds of the plant (Baltaev and Abubakirov, 1988; Girault et al., 1988; Baltaev, 1992a,b, 1995; Pis et al., 1994; Baltaev et al., 1997; Ramazanov et al., 1997a,b; Sadykov et al., 1997; Borovikova and Baltaev, 1999; Borovikova et al., 1999; Vokac et al., 2002; Budesinky et al., 2008). Several sterols, such as β-sitosterol, stigmasterol, Δ7-avenasterol, campesterol, and cholesterol have been detected in the roots (Khomova et al., 1995) and cholesterol, stigmasterol, β-sitosterol, and β-sitostanol in seeds of the plant (Stransky et al., 1998). The structures of ecdysteroids, shown as Fig. 3, were verified using The Ecdysone Handbook (Lafont et al., 2002).

Regarding *R. carthamoides* phenolic compounds, several authors reported the presence of various flavonoids or anthocyanins (Table 2, Fig. 4) in the roots, aerial parts and inflorescences of the plant (Vereskovskii and Chekalinskaya, 1979; Vereskovskii, 1980a,b; Dombi et al., 1989; Varga et al., 1990; Faizieva et al., 1999; Sharaf et al., 2001; Miliauskas et al., 2005; Koleckar et al., 2008a,b). Hajdu et al. (1998) isolated (*E*)-3,3′-dimethoxy-4,4′-dihydroxystilbene (**108**), a substance biogenetically closely related to flavonoids, from the roots of the plant. Besides the flavonoids, a number of phenolic acids (Vereskovskii and Chekalinskaya, 1978; Skiba and Werglarz, 1999, 2003), several lignans (Harmatha and Dinan, 2003; Harmatha et al., 2007), such as carthamogenin (**103**), carthamoside (**104**), trachelogenin (**105**), or tracheloside (**106**), and tannins e.g. ellagic acid (**107**) have also been detected in both underground and aerial parts of the species. Recently, the serotonin phenylpropanoids, namely *N-(Z)*-feruoylserotonin (**99**), *N-(Z)*-isoferuoylserotonin (**100**), *N-(E)*-feruoylserotonin (**101**), and *N-(E)*-isoferuoylserotonin

Fig. 2. *R. carthamoides* plants in flower (Original photo by M. Grbavcic).

(**102**), have been isolated from the seeds (Pavlik et al., 2002; Harmatha et al., 2007). The structures of phenolic acids (Table 3) and other phenol compounds of *R. carthamoides* are shown as Fig. 5.

In regard to other groups of compounds found in *R. carthamoides*, various polyacetylenes (**109**–**113**) and sesquiterpene lactones as cynaropicrin (**114**), repdiolide (**115**), chlorojanerin (**116**), repensolide (cebellin E) (**117**), and janerin (**118**) have been isolated from roots of the plant (Szendrei et al., 1984; Nowak, 1992; Chobot et al., 2003). Vereskovskii et al. (1978) have found triterpenoid glycosides, namely rhaponticosides A, B, C, D, E, F, G and H in the roots and aerial parts of *R. carthamoides*. Triterpenoid components reported from the literature for underground parts of the plant are parkeol (**119**) and parkeyl acetate (**120**), known also as carthamenol and carthamenyl acetate, respectively (Grimshaw et al., 1981; Khalid et al., 1989). Fig. 6 includes various structures of the miscellaneous compounds mentioned above.

Although essential oil is sometimes mentioned among chemical components of *R. carthamoides*, there are only few reports dealing with its detailed analysis. In one of the earlier reports, Yankulov (1962) observed the presence of essential oil in underground organs with a concentration of up to 0.2%. Recently, Geszprych and Weglarz (2002) reported a content of essential oil in dried plant material ranging from 0.07% to 0.11% and from 0.08% to 0.09% in underground organs and leaves, respectively. The monoterpenes, predominated by geraniol (17.04–18.27%), were the most abundant in the essential oil from roots and rhizomes, whereas sesquiterpenes, represented by β-caryophyllene (24.65–32.30%), was identified as the most important compound in the leaves analysed in their study. A relatively high percentage of linalool (8.88–12.07%) in rhizomes and roots and neeral (8.12–10.22%) in leaves was also observed. In contrast to previous reports, the results of our recently published analysis of the essential oil obtained

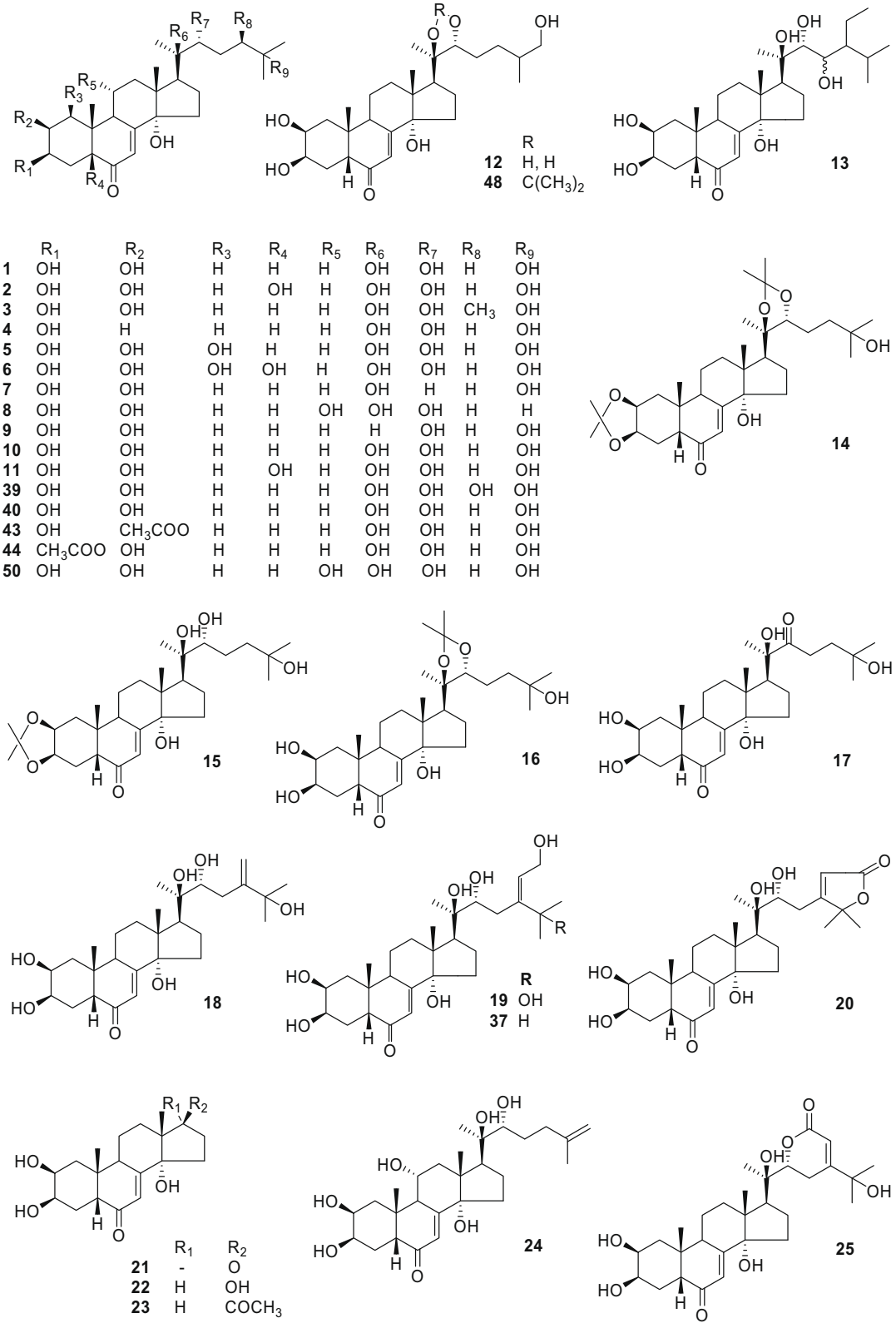
Table 1
Ecdysteroid compounds of R. carthamoides.

Structure number	Compound name	Plant parts	References
1	20-Hydroxyecdysone	Root, aerial part, seed	Krasnov et al. (1977), Yakubova and Sakharova (1980), Varga et al. (1986), Baltaev and Abubakirov (1988), Girault et al. (1988), Pis et al. (1994), Repcak et al. (1994), Ramazanov et al. (1997a), Timofeev et al. (1998), Budesinky et al. (2008)
2	Polypodine B	Root	Baltaev and Abubakirov (1988), Girault et al. (1988), Pis et al. (1994)
3	Makisterone A	Root	Pis et al. (1994)
4	2-Deoxyecdysterone	Root	Baltaev and Abubakirov (1988)
5	Integristerone A	Root	Baltaev and Abubakirov (1988), Vokac et al. (2002), Budesinky et al. (2008)
6	Integristerone B	Root	Vokac et al. (2002)
7	Taxisterone	Root	Vokac et al. (2002)
8	Ajugasterone C	Root	Szendrei et al. (1988), Pis et al. (1994), Budesinky et al. (2008)
9	α-Ecdysone	Seed	Sadykov et al. (1997), Budesinky et al. (2008)
10	Lesterone	Seed	Borovikova and Baltaev (1999)
11	Rapisterone D	Seed	Baltaev (1995)
12	Inokosterone	Root	Krasnov et al. (1977), Budesinky et al. (2008)
13	Rapisterone	Root	Baltaev and Abubakirov (1988)
14	20-Hydroxyecdysone 2,3;20,22-diacetonide	Root	Pis et al. (1994)
15	20-Hydroxyecdysone 2,3-monoacetonide	Root	Baltaev and Abubakirov (1988)
16	20-Hydroxyecdysone 20,22-monoacetonide	Root	Baltaev and Abubakirov (1988), Pis et al. (1994)
17	22-Oxo-20-hydroxyecdysone	Root	Vokac et al. (2002)
18	24(28)-Dehydromakisterone A	Root, aerial part, seed	Baltaev and Abubakirov (1988), Girault et al. (1988), Ramazanov et al. (1997a), Budesinky et al. (2008)
19	(24Z)-29-Hydroxy-24(28)-dehydromakisterone C	Root	Vokac et al. (2002), Budesinky et al. (2008)
20	Carthamosterone	Root, aerial part	Vokac et al. (2002), Girault et al. (1988)
21	Rubrosterone	Root	Vokac et al. (2002)
22	Dihydrorubrosterone	Root	Vokac et al. (2002)
23	Posterone	Root	Vokac et al. (2002)
24	Isovitexirone	Root	Pis et al. (1994), Vokac et al. (2002)
25	Leuzeasterone	Root	Vokac et al. (2002)
26	Makisterone C	Root, aerial part	Girault et al. (1988), Vokac et al. (2002), Budesinky et al. (2008)
27	Polypodine B 20,22-acetonide	Root	Pis et al. (1994)
28	Rapisterone B	Seed	Baltaev (1992a)
29	Rapisterone C	Seed	Baltaev (1992b)
30	Rapisterone D 20-acetate	Seed	Borovikova et al. (1999)
31	24(24′)[Z]-Dehydroamarasterone B	Seed	Baltaev et al. (1997)
32	Polypodine B-22-benzoate	Seed	Sadykov et al. (1997)
33	Carthamosterone A	Seed	Ramazanov et al. (1997a)
34	Carthamosterone B	Seed	Ramazanov et al. (1997b)
35	Amarasterone A	Root	Budesinky et al. (2008)
36	Carthamoleusterone	Root	Budesinky et al. (2008)
37	24(28)-Dehydroamarasterone B	Root	Budesinky et al. (2008)
38	22-Deoxy-28-hydroxymakisterone C	Root	Budesinky et al. (2008)
39	3-Epi-20-hydroxyecdysone	Root	Vokac et al. (2002)
40	24-Epi-makisterone A	Root	Budesinky et al. (2008)
41	14-Epi-ponasterone A 22-glucoside	Root	Budesinky et al. (2008)
42	5-α-20-Hydroxyecdysone	Root	Vokac et al. (2002)
43	20-Hydroxyecdysone 2-acetate	Root	Budesinky et al. (2008)
44	20-Hydroxyecdysone 3-acetate	Root	Budesinky et al. (2008)
45	1β-Hydroxymakisterone C	Root	Budesinky et al. (2008)
46	26-Hydroxymakisterone C	Root	Budesinky et al. (2008)
47	15-Hydroxyponasterone A	Root	Budesinky et al. (2008)
48	Inokosterone 20,22-acetonide	Root	Budesinky et al. (2008)
49	Integristerone A 20,22-acetonide	Root	Budesinky et al. (2008)
50	Turkesterone	Root	Budesinky et al. (2008)

by steam distillation from *R. carthamoides* fresh roots using a Clevenger-type apparatus, showed a predominant content of sesquiterpenes, whereas 13-norcypera-1(5),11(12)-diene, cyperene and aliphatic compound aplotaxene were identified as three major constituents of the oil (Havlik et al., 2009). These discrepancies suggest that further investigation of the chemical composition of *R. carthamoides* essential oils could provide interesting information regarding the chemistry of this species.

3. Biological activities

Brekhman and Dardymov (1969) classified *R. carthamoides* as an adaptogen, a term currently used by herbalists to refer to a natural herb product which increases the body's resistance to stresses such as trauma, anxiety and bodily fatigue (Winston and Maimes, 2007). As is summarized below, the experimental pharmacological and clinical investigations carried out during the last 25 years have shown that extract and individual compounds (especially ecdysteroids) isolated from different parts of the plant have specific biological effects indicating it has marked adaptogenic properties including immunostimulation, eliminating free radicals to prevent oxidizing pathology, increasing protein biosynthesis and physical work capacity along with endurance and performance, enhancing cardiovascular functions and mental work capacity. However, since there is a similarity between some of the ascribed properties of the plant and those ascribed to ecdysteroids, reading of additional literature focusing information on general biological properties of the ecdysteroid compounds, such as review of Lafont and Dinan (2003), is advisable in order to obtain a better understanding of the complete pharmacological potential of the plant.



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
1	OH	OH	H	H	H	OH	OH	H	OH
2	OH	OH	H	OH	H	OH	OH	H	OH
3	OH	OH	H	H	H	OH	OH	CH_3	OH
4	OH	H	H	H	H	OH	OH	H	OH
5	OH	OH	OH	H	H	OH	OH	H	OH
6	OH	OH	OH	OH	H	OH	OH	H	OH
7	OH	OH	H	H	H	OH	H	H	OH
8	OH	OH	H	H	OH	OH	OH	H	H
9	OH	OH	H	H	H	H	OH	H	OH
10	OH	OH	H	H	H	OH	OH	H	OH
11	OH	OH	H	OH	H	OH	OH	H	OH
39	OH	OH	H	H	H	OH	OH	OH	OH
40	OH	OH	H	H	H	OH	OH	H	OH
43	OH	CH_3COO	H	H	H	OH	OH	H	OH
44	CH_3COO	OH	H	H	H	OH	OH	H	OH
50	OH	OH	H	H	OH	OH	OH	H	OH

Fig. 3. The structures of *R. carthamoides* ecdysteroid compounds.

3.1. Effect on proteosynthesis and work capacity

Various *in vivo* tests with animals and clinical tests performed on athletes mainly in the former Soviet Union and Russian Federation countries proved a significant positive effect of *R. carthamoides* extracts and ecdysteroid constituents (especially of 20E) on the increase of protein synthesis and working capacity of tested subjects, subsequently leading to the development of several formulations used to increase strength, endurance and promote muscle growth of athletes (Gadzhieva et al., 1995; Azizov, 1997; Azizov et al., 1997, 1998).

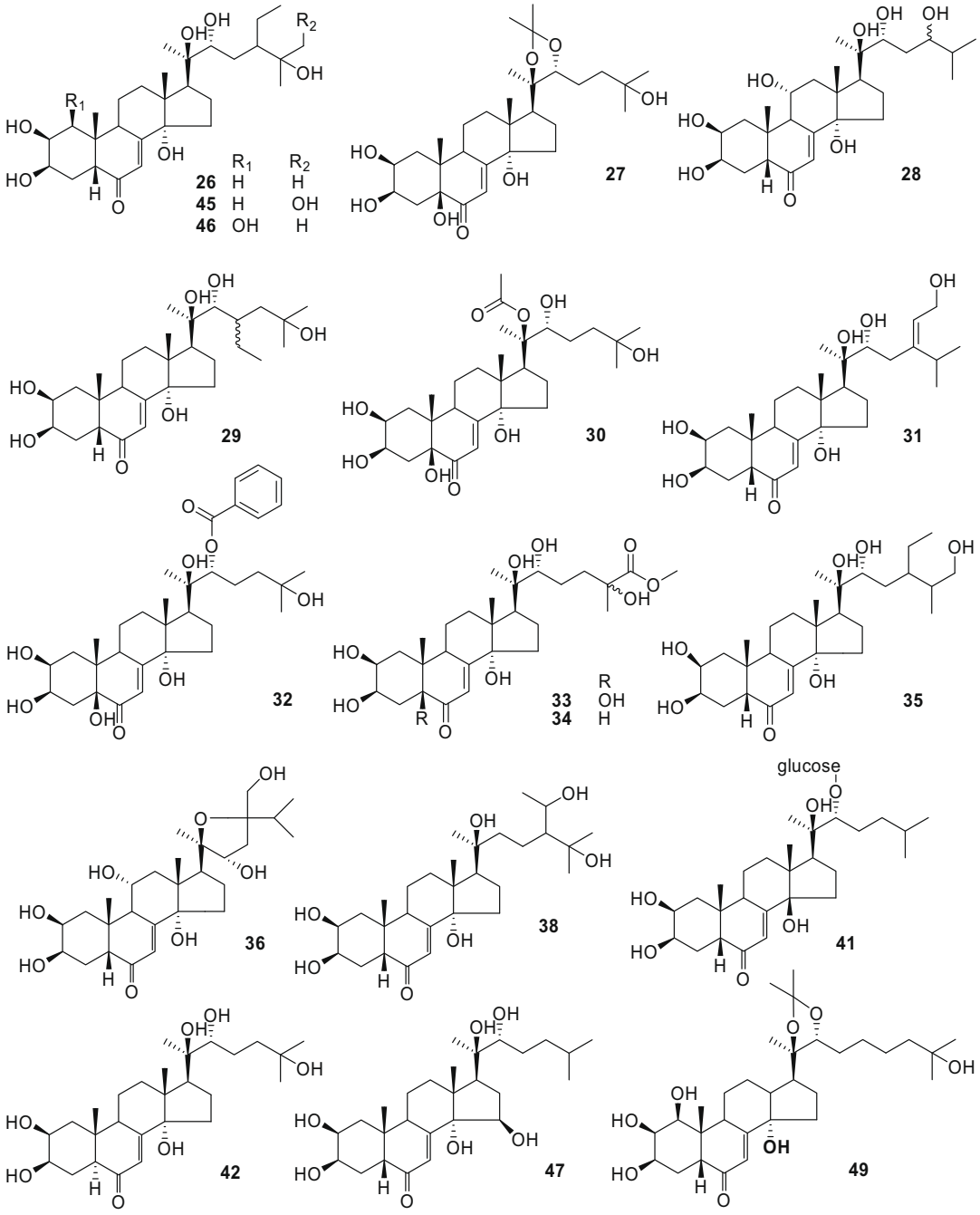


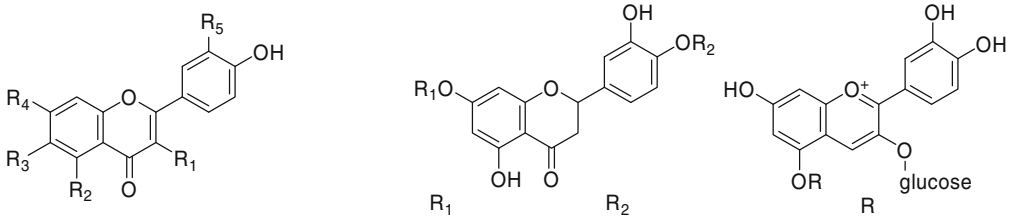
Fig. 3 (*continued*)

Since the 1970s, the anabolic effect of *R. carthamoides* has been reported in a number of experiments on laboratory animals, performed mainly with mice or rats. According to the results of earlier experiments of Syrov and Kurmukov (1976), it is evident that an introduction of *R. carthamoides*-derived 20E at a dose of 5 mg/kg administered to rats for 7 days is shown to be accompanied by an increase in the weight of the liver, heart, kidneys and musculus tibialis anterior. In another study, it was found that 20E isolated from *R. carthamoides* applied daily as intraperitoneal injections to mice, enhanced growth in the groups of female juveniles but not in the male ones; however, it caused increased growth in both males and females adults (Stopka et al., 1999). Growth-promoting effects of *R. carthamoides* derived 20E have also been latterly reported in experiments with Japanese quails (Slama et al., 1996) and pigs (Kratky et al., 1997). A significant increase of the living mass of freshly hatched Japanese quails was found after 37 days of feeding on a diet containing graded mounts of pulverized seeds of *R. carthamoides* containing 20E (Koudela et al., 1995). In an experiment with male albino mice running on a treadmill, an increase of working capacity (56%) was observed on the 20th day of training after oral administration of *R. carthamoides* extract and a Leveton preparation (consisting of *R. carthamoides* root, bee pollen and vitamins C and E). Similarly, in a swimming endurance test both preparations significantly increased the swimming duration of male albino rats (Azizov and Seifulla, 1998). In more recent studies, Todorov et al. (2000a,b) observed that intraperitoneal injections of aqueous solutions of *R. carthamoides* extract and 20E activates the biosynthesis of macromolecules (protein, RNA, and DNA) in organs of mice.

In clinical trials, preparations named Ecdysten (active ingredient 20E), Leveton and Prime Plus (combination of Ecdysten, unrefined

Table 2
Flavonoids and related compounds of *R. carthamoides*.

Structure number	Compound name	Plant parts	References
51	6-Hydroxykaempferol-7-*O*-(6″-*O*-acetyl-β-D-glucopyranoside)	Aerial part	Koleckar et al. (2008b)
52	Patuletin	Aerial part	Varga et al. (1990), Koleckar et al. (2008b)
53	6-Hydroxykaempferol-7-glukoside	Aerial part	Varga et al. (1990)
54	Quercetagitrin	Aerial part	Varga et al. (1990)
55	6-Methoxykempferol	Aerial part	Varga et al. (1990)
56	Quercetin-5-glucoside	Aerial part, root	Varga et al. (1990)
57	Isorhamnetin-5-glucoside	Aerial part, root	Varga et al. (1990)
58	Quercetin-3,3′-dimethyl ether	Aerial part, root	Dombi et al. (1989), Varga et al. (1990)
59	Quercetin	Root	Vereskovskii (1980a), Varga et al. (1990), Faizieva et al. (1999)
60	Quercetagetin	Root	Vereskovskii (1980a), Faizieva et al. (1999)
61	Luteolin	Inflorescence, root	Vereskovskii (1980a), Vereskovskii (1980b), Faizieva et al. (1999)
62	Kaempferol	Root	Vereskovskii (1980a), Faizieva et al. (1999)
63	Isorhamnetin	Root	Vereskovskii (1980a), Varga et al. (1990), Faizieva et al. (1999)
64	Quercetin-3-methyl ether	Inflorescence, root	Vereskovskii (1980b), Dombi et al. (1989), Varga et al. (1990)
65	Quercetine-5-*O*-β-D-galactoside	Root	Sharaf et al. (2001)
66	Isorhamnetine 5-*O*-α-L-rhamnoside	Root	Sharaf et al. (2001)
67	Quercetagetin-7-*O*-β-glucopyranoside	Root	Miliauskas et al. (2005)
68	6-Hydroxykaempferol-7-*O*-β-glucopyranoside	Root	Miliauskas et al. (2005)
69	Quercetagetin-7-*O*-(6″-*O*-acetyl-β-glucopyranoside)	Root	Miliauskas et al. (2005)
70	6-Methoxykaempferol-3-*O*-β-glucopyranoside	Root	Miliauskas et al. (2005)
71	6-Hydroxykaempferol-7-*O*-(6″-*O*-acetyl-β-D-glucopyranoside)	Root	Miliauskas et al. (2005)
72	Quercimeritrin	Root	Varga et al. (1990)
73	Apigenin	Inflorescence	Vereskovskii (1980b)
74	Eriodictyol	Aerial part	Koleckar et al. (2008b)
75	Eriodictyol-7-β-glucopyranoside	Aerial part	Koleckar et al. (2008b)
76	Hesperetin	Root	Faizieva et al., 1999
77	Chrysanthemin	Inflorescence, root	Vereskovskii and Chekalinskaya (1979), Faizieva et al. (1999)
78	Cyanin	Inflorescence, root	Vereskovskii and Chekalinskaya (1979), Faizieva et al. (1999)



	R_1	R_2
74	H	H
75	glucopyranose	H
76	H	CH_3

	R
77	H
78	glucose

	R_1	R_2	R_3	R_4	R_5
51	OH	OH	OH	O-(6"-acetyl) glucopyranose	H
52	OH	OH	OCH_3	OH	OH
53	OH	OH	OH	O-glucose	H
54	OH	OH	OH	O-glucose	OH
55	OH	OH	OCH_3	OH	H
56	OH	O-glucose	H	OH	OH
57	OH	O-glucose	H	OH	OCH_3
58	OCH_3	OH	H	OH	OCH_3
59	OH	OH	H	OH	OH
60	OH	OH	OH	OH	OH
61	H	OH	H	OH	OH
62	OH	OH	H	OH	H
63	OH	OH	H	OH	OCH_3
64	OCH_3	OH	H	OH	OH
65	OH	O-galactose	H	OH	OH
66	OH	O-rhamnose	H	OH	OCH_3
67	OH	OH	OH	O-glucopyranose	OH
68	OH	OH	OH	O-glucopyranose	H
69	OH	OH	OH	O-(6"-acetyl) glucopyranose	OH
70	O-glucopyranose	OH	OCH_3	OH	H
71	OH	OH	OH	(6"-acetyl) glucopyranose	H
72	OH	OH	H	O-glucose	OH
73	H	OH	H	OH	H

Fig. 4. The structures of flavonoid compounds of *R. carthamoides*.

Table 3
Phenolic acids of *R. carthamoides*.

Structure number	Compound name	References
79	Benzoic acid	Skiba and Weglarz (2003)
80	*m*-Hydroxybenzoic acid	Skiba and Weglarz (2003)
81	*p*-Hydroxybenzoic acid	Skiba and Weglarz (2003)
82	Salicylic acid	Skiba and Weglarz (2003)
83	Protocatechuic acid	Vereskovskii and Chekalinskaya (1978), Skiba and Weglarz (2003)
84	Gentisic acid	Skiba and Weglarz (2003)
85	Vanillic acid	Vereskovskii and Chekalinskaya (1978), Skiba and Weglarz (2003)
86	Gallic acid	Skiba and Weglarz (2003)
87	Syringic acid	Skiba and Weglarz (2003)
88	*o*-Coumaric acid	Skiba and Weglarz (2003)
89	*p*-Coumaric acid	Vereskovskii and Chekalinskaya (1978), Skiba and Weglarz (2003)
90	Caffeic acid	Vereskovskii and Chekalinskaya (1978), Skiba and Weglarz (2003)
91	Ferulic acid	Vereskovskii and Chekalinskaya (1978), Skiba and Weglarz (2003)
92	Sinapic acid	Skiba and Weglarz (2003)
93	*o*-Hydroxyphenylacetic acid	Skiba and Weglarz (2003)
94	*p*-Hydroxyphenylacetic acid	Skiba and Weglarz (2003)
95	Chlorogenic	Vereskovskii and Chekalinskaya (1978), Skiba and Weglarz (2003)
96	Neochlorogenic	Vereskovskii and Chekalinskaya (1978)
97	Isochlorogenic acid a	Vereskovskii and Chekalinskaya (1978)
98	Isochlorogenic acid b	Vereskovskii and Chekalinskaya (1978)

With exception of *o*-coumaric acid detected in aerial part only, all phenolic acids were found in both aerial and underground parts of the plant.

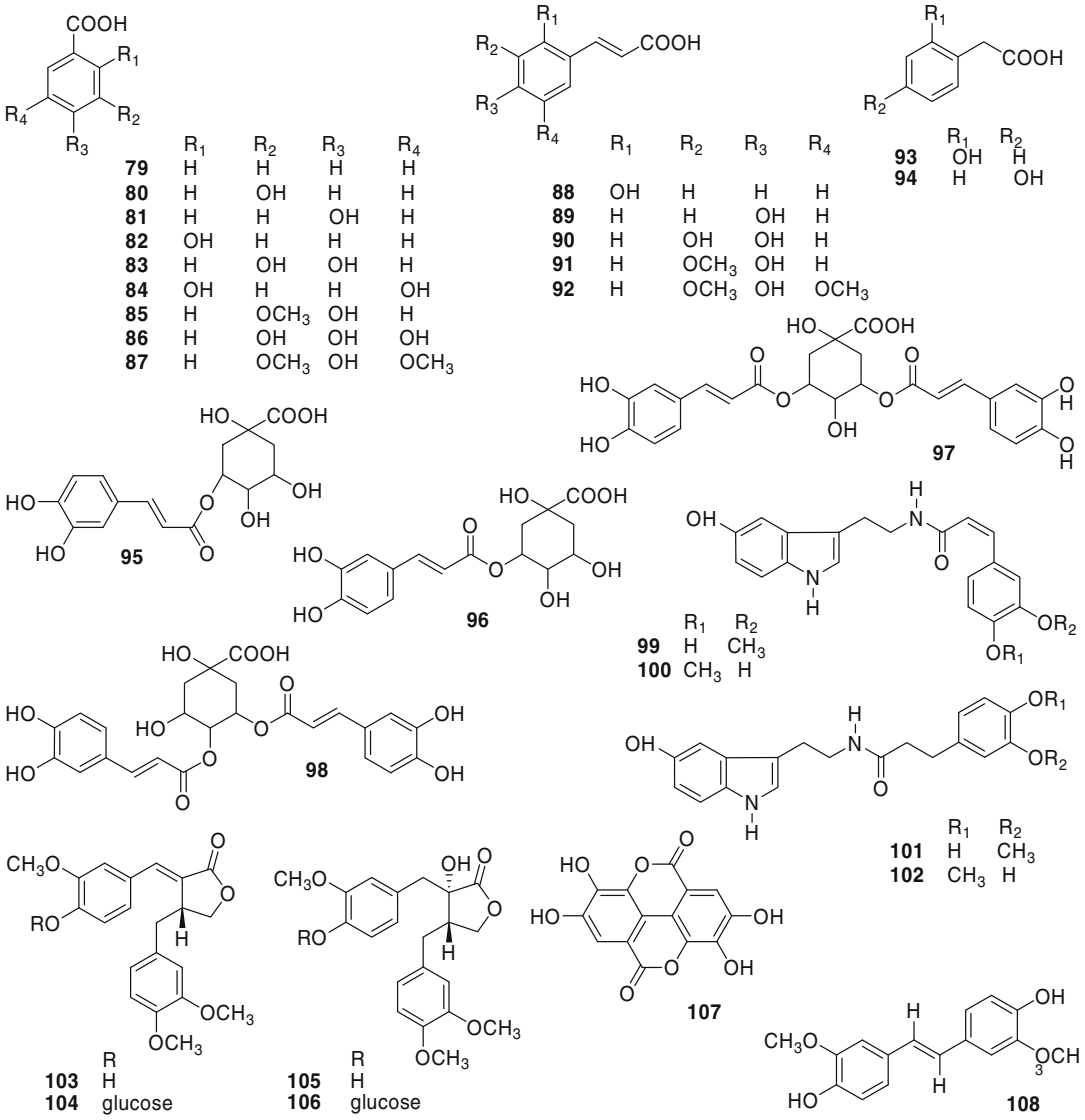


Fig. 5. The structures of phenolic acids, tannins and lignans of *R. carthamoides*.

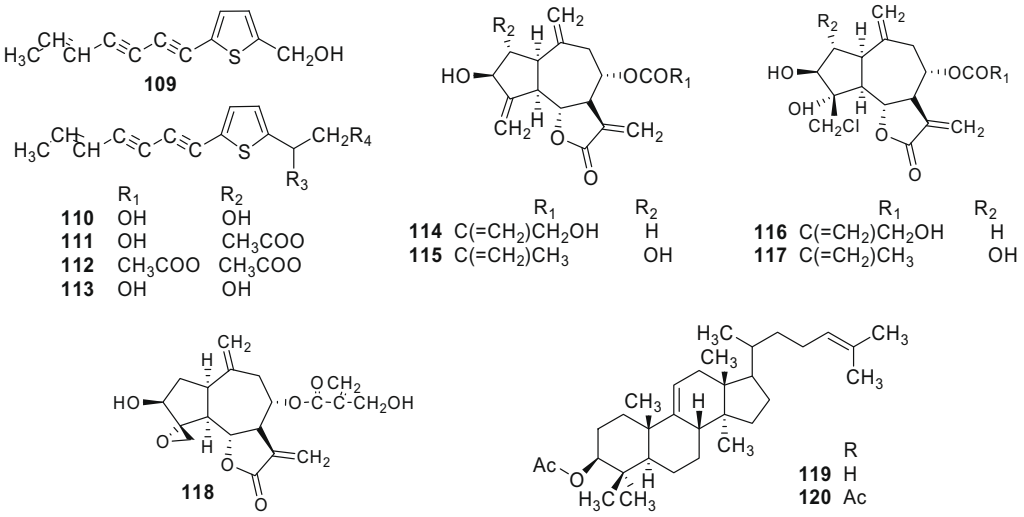


Fig. 6. Miscellaneous compounds of *R. carthamoides*.

sugar and casein) taken orally for 20 days by three separated groups of track-and-field athletes under conditions of daily aerobic-anaerobic training significantly diminished fat content and elevated the muscle mass in all groups of treated individuals in comparison with the control group (Gadzhieva et al., 1995). Further studies performed over a 20-day administration of *R. carthamoides* tincture and Leveton caused a marked reduction of the blood coagulation potential accompanied with an increase in the working capacity and rehabilitation of top athletes under intensive physical activity (Azizov, 1997). It also possessed an effect on the humoral immunity of track and field runners, whereas treatment with both preparations significantly contributed to restoration of the lowered immunoglobulins A (IgA) and G (IgG), as well as of the complement component 3 concentration in blood serum. Furthermore it increased working capacity by 10% to 15% (Azizov et al., 1997). A subsequent study showed that a 20-day administration of Leveton reduced the level of malonic dialdehyde in the urine of highly skilled athletes and increased their physical working capacity in bicycle ergometry exercise tests with gradually increasing physical loads (Azizov et al., 1998).

3.2. Influence on cardiovascular system and blood

Considering experiments on the cardiovascular system and blood characteristics, Petkov et al. (1984) demonstrated that the dried residue of ethanol (40%) extract re-dissolved in saline and administrated intraduodenally to chloralose-anesthetized male cats in a dose of 200 mg/kg exerted a significant decrease in blood pressure by 25–30% as compared to control group of animals. Per os administration of 20E at a dose of 5 mg/kg markedly stimulated secretion and improved chemical characteristics of bile because of decreased cholesterol content and increased levels of bile acids and bilirubin in normal rats; moreover, it exerts more beneficial parameters when studied in rats with toxic hepatitis induced by heliotrine (Syrov et al., 1986). The root ethanol extract exhibited marked antidiabetic properties by decreasing the blood level of glucose and increasing the reduced level of liver glycogen in experiments on mice and rats with alloxan-induced diabetes (Molokovskii et al., 1989). A dry extract was studied for the haemorheological activity in spontaneous hypertensive rats. A 5-day treatment of the test rats with acute myocardial infarction, given a daily dose of 150 mg/kg, improved rheological characteristics of blood such as reduced viscosity of whole blood and plasma, increased spontaneous erythrocyte aggregation and fibrinogen concentration and increased erythrocyte deformability and electrophoretic mobility (Plotnikov et al., 1999, 2001). Repeated prophylactic administration of plant adaptogen preparation based on extract from *R. carthamoides* produced a pronounced anti-arrhythmic effect on the model of adrenal arrhythmia in rats (Maimeskulova and Maslov, 2000). A recent study has also demonstrated insulin-stimulating and antihyperglycaemic activities (Molokovskii et al., 2002). Repeated administration of *R. carthamoides* derived 20E increased the content of erythrocytes and haemoglobin in the blood and cause a marked effect on red blood regeneration in haemotoxic phenylhydrazine anaemia in rats (Syrov et al., 1997). A preparation consisting of flavonoids isolated from *R. carthamoides* namely hesperetin, quercetin, quercetagetin, luteolin, kaempferol, isorhamnetin, chrysanthemin and cyanin has been found to prevent the accumulation of cholesterol and triglycerides in triton WR 1339 induced hyperlipidemic rats (Khushbaktova and Syrov, 1989). In a further study, *R. carthamoides* flavonoids substantially diminished the manifestations of an atherosclerotic process in rabbits, whereas their therapeutic effect was associated both with the hypolipidemic activity and the capacity of flavonoids to inhibit local mechanisms of atherogenesis, enhancing vascular wall resistance (Khushbaktova et al., 1991). Recently, *in vitro* antiplatelet activity of crude ethanol extract and flavonoids from aerial parts of *R. carthamoides* was determined in human platelet-rich plasma. Arachidonic acid (AA), adenosine diphosphate (ADP), collagen (COL), and thrombin were used as agonists of platelet aggregation. The summary extract showed a significant inhibition of the aggregation induced by COL and ADP. Of the tested flavonoids, eriodictyol and patuletin influenced COL- and AA-induced aggregation (Koleckar et al., 2008a).

The data from a number of *in vivo* studies summarised above demonstrated a significant positive effect of *R. carthamoides* derived extracts, 20E and flavonoids on the cardiovascular system and blood characteristics in animal models with various induced or spontaneous disorders such as atherosclerosis, anti-arrhythmia, diabetes, myocardial infarction and hepatitis.

3.3. Effect on nervous system and brain

As shown later in this section, several *in vivo* tests with rats or rabbits showed a significant effect of various extracts, ecdysteroids and *N*-feruloylserotonin isomers isolated from *R. carthamoides* on mammalian nervous systems. In one of several studies, the water–ethanol extract from roots injected as a saline solution at

500 mg/kg doses increased the locomotor activity, showed a clear-cut tendency towards antagonizing the narcotic effects of chloral hydrate and towards increasing CNS excitability (jumping test), and also improved the learning and memory indices in rats 60 min before training (Petkov et al., 1984). The root ethanol extract demonstrated a significant improvement in learning and memory ability, as well as completely eliminating the scopolamine-induced memory impairment using the maze-training method of active avoidance with punitive reinforcement in experiments with rats (Mosharrof, 1987). The oral administration of 150 mg/kg of dried *R. carthamoides* root extract prepared by extraction with 40% ethanol to rats with cerebral ischaemia for 5 days prevented destructive changes and decreased the density of synapses in the cerebral cortex (Logvinov et al., 2001). The administration of Ecdysten at doses of 5–10 mg/kg to rabbits resulted in an expressed activation of animal EEG and exerts an awakening effect, reducing natrium thiopental and chloralosa induced hypnosis. This preparation produced an antihypnotic effect by reducing animal sleep in the experiments with mice in combined administration with chloral hydrate and hexenal. Additionally, multiple administrations of Ecdysten to rats stimulated their emotional and research activity, shortening the time of conditioned defence reflex development (Syrov and Khushbaktova, 2005). As recently reported by Yamamotova et al. (2007), the *N*-feruloylserotonins rich fraction isolated from seeds of *R. carthamoides* possessed selective stress-reducing effects in rats with pre-existing tendencies toward anxiety.

In only one study on the nervous system performed with human subjects, a decoction of *R. carthamoides* root (half glass, 4–5 times a day during 2 month) promoted a correction of the depressive manifestation in alcoholics with depressive states, and also improved health conditions of patients with gastrointestinal pain of somatic origin. The decoction was prepared in the following manner: boiling water was poured into a glass containing a tablespoon of pulverized plant material and additionally boiled for 30 min in laboratory water bath, then cooled at room temperature for 10 min, filtered, topped up with water to the full volume of the glass and flavoured with teaspoon of honey (Ibatov, 1995).

3.4. Effect on reproduction and sexual function

The aphrodisiacal reputation of the plant has been studied in several experiments demonstrating the positive influence of 20E on sexual functions of human subjects, but at the same time, showing inconsistent results in tests on animals. For example, Mirzaev et al. (2000) reported that a 10-day administration of 20E (5 and 10 mg/kg) significantly improved the behavioural characteristics of the sexual function of rats, whereas in experiments performed by Stopka et al. (1999), daily peritoneal injections of 20E isolated from *R. carthamoides* inhibited the production of sperm in male and caused disturbances of the oestrous cycles in the female mice. In trials with humans, the administration of Ecdysten to men with an infertility diagnosis (disturbed spermatogenesis as a complication of some urologic diseases) increased the copulative function and improved the sperm quality as well as improved sexual function of patients in the stage of recovery after myocardial infarction (Mirzaev et al., 2000).

3.5. Anti-oxidative, immunomodulatory and anticancerogenic activity

In a great number of *in vitro* tests, Miliauskas et al. (2004) have screened acetone, ethyl acetate and methanol extracts of 12 medicinal and aromatic plants for its radical scavenging activity (RSA) using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Among all extracts tested, high RSA was observed for a methanol extract from leaves and stems of *R. carthamoides* in both assays. The high radical scavenging ability was evidently caused by a high content of polyphenolic compounds such as flavonoids and flavonols. A hyphenated LC-DAD-SPE-NMR setup in combination with on-line radical scavenging detection has subsequently been applied for the identification of radical scavenging compounds of *R. carthamoides* aerial parts. The analysis led to the discovery of a new compound 6-hydroxykaempferol-7-*O*-(6″-*O*-acetyl-β-D-glucopyranoside), however the results of the DPPH test showed that its radical scavenging activity was weaker than that of the reference antioxidants rosmarinic acid and Trolox (Miliauskas et al., 2005). In a study performed by Biskup and Eojkowska (2006), aqueous and methanol leaf extracts exhibited RSA towards DPPH (IC_{50} = 25 and 45 μg/ml, respectively) and turned out to be more effective than BHT (IC_{50} = 190 μg/ml), but less effective than ascorbic acid and α-tocopherol (IC_{50} = 4 and 12 μg/ml, respectively). In a recent comparative study, Koleckar et al. (2008b) assayed 88 extracts from various parts of plants from European Asteraceae and Cichoriaceae for radical scavenging activity by means of DPPH. Among all samples tested the extract from the leaves of *R. carthamoides* (IC_{50} = 0.046 mg/ml) was chosen as the most promising material for a subsequent phytochemical study, which resulted in isolation of seven different compounds. Their antioxidant activity was evaluated by DPPH and ferric reducing antioxidant power (FRAP) tests and compared with Trolox and quercetin. Both tests evaluated 6-hydroxykaempferol-7-*O*-(6″-*O*-acetyl-β-D-glucopyranoside) as the most active antioxidant.

The polysaccharide-rich fraction from the fresh leaves markedly enhanced phytohemagglutinin-induced proliferation of human lymphocytes up to a concentration of 150 μg/ml and significantly decreased the release of oxygen free radicals by human granulocytes *in vitro* indicating that the plant contains constituents endowed with immunomodulatory activity (Lamer-Zarawska et al., 1996). In a recent paper by Harmatha et al. (2008) discussing the lack of immunostimulatory activity of ecdysteroids, namely 20E, polypodine B, ajugasterone C, inokosterone, makisterone A, carthamosterone, poststerone, rubrosterone and dihydrorubrosterone, the authors suggest that classes of substances other than ecdysteroids, e.g. lignans, flavonoids or sesquiterpene lactones are more likely responsible for the immunopharmacological effect of the plant.

Hamburger et al. (2006) recently reported that lipophilic root extract exhibited effects on the proliferation of human breast cancer cell line MCF-7, whereas 20E was found to be inactive. In another study, chloroform, methanol, and aqueous leaf extract, as well as pure 20E, exhibited no, or only mild, cytotoxic activity against HeLa (cervical carcinoma) and HL-60 (leukaemia) cell lines, using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (Biskup and Eojkowska, 2006).

One of the rare *in vitro* studies addressing the effect on immunological characteristics found that the combination of *R. carthamoides* extract and sarcolysin inhibited the process of lympholeucosis in mice (Vershinina, 1967). Results of more recent research showed that a preparation based on *R. carthamoides* root extract possessed an inhibitory effect on the carcinogenesis induced by transplacental administration of *N*-nitrosylurea. Yearlong administration of the drug was followed by a higher survival rate of the rats and a lower occurrence and/or multiplicity of tumours, mainly those of the central nervous system (Bespalov et al., 1992).

In a human clinical study, a plant preparation called AdMax, a combination of dried ethanol/water extracts from roots of *R. carthamoides*, *Rhodiola rosea*, *Eleutherococcus senticosus* and fruits of *Schizandra chinensis*, was studied by Kormosh et al. (2006) with respect to its influence on the immunity in ovarian cancer patients. Twenty eight patients with stage III–IV epithelial ovarian cancer were treated once with 75 mg/m^2 cisplatin and 600 mg/m^2 cyclophosphamide. Peripheral blood was collected 4 weeks after

chemotherapy. Subclasses of T, B and NK lymphocytes as well as immunoglobulin M (IgM), IgA and IgG concentrations were tested in the blood samples. In patients who took AdMax (270 mg a day) for 4 weeks following chemotherapy, the mean numbers of the four T cell subclasses were increased in comparison to the mean numbers of the T cell subclasses in patients who did not take AdMax. In patients who took AdMax, the mean amounts of IgG and IgM were also increased. The obtained results suggest that the combination of extracts from adaptogenic plants (including *R. carthamoides*) may boost the suppressed immunity in ovarian cancer patients who are subject to chemotherapy.

In summary, the above mentioned data shows that the results of various *in vitro* assays performed with *R. carthamoides* extracts and their fractions or individual compounds, such as lignans or flavonoids, suggest promising antioxidantive, immunomodulary and anticancerogenic properties of the plant, however only few of them have been further investigated using *in vivo* or clinical studies.

3.6. Antimicrobial and antiparasitic activity

The *in vitro* inhibitory effect of various crude extracts from roots or aerial parts of *R. carthamoides* on Gram-positive bacteria, e.g. *Bacillus cereus*, *Staphylococcus epidermidis*, *Bacteroides fragilis* (Kokoska et al., 2002, 2005) and some fungi (Jahodar et al., 2003) have previously been observed. The lipid fraction from seeds has demonstrated antimicrobial activity against *Proteus vulgaris, Aspergillus niger* and *Penicillium verrucosum* (Shirshova et al., 1999). In our experiments, ethyl acetate fraction obtained from *R. carthamoides* aerial part inhibited *in vitro* growth of 19 different strains of *Staphylococcus aureus*, with minimum inhibitory concentrations (MICs) ranging from 128 to 512 μg/ml. This fraction exhibited potent activity against clinical isolates, which showed an associated resistance to oxacillin, ciprofloxacin and erythromycin (Janovska et al., 2008). The thiophene polyene (*E*)-2-[5-(hept-5-en-1,3-diynyl)-thien-2-yl]-ethan-1,2-diol isolated from ethanol extract of underground parts demonstrates significant antifungal activity mainly against *Candida glabrata, Aspergillus fumigatus* and *Trichophyton mentagrophytes* var. *mentagrophytes* with MICs ranging from 4 to 32 μg/ml. The activity after 24 h of incubation against *A. fumigatus* and *Candida tropicalis* was ½ and ¼ of the effect of ketoconazole, respectively (Chobot et al., 2003).

Regarding the anti-infective actions of *R. carthamoides*, there has only been one study performed with human subjects. As a result of this trial, the preparation Ecdysten has shown significant efficacy in the treatment of patients with persistent and acute giardiasis (Osipova et al., 2002).

Since growth inhibitory action of 20E on bacteria and fungi was observed at rather high concentrations ranging between 100 and 400 μg/ml (Ahmad et al., 1996), some other effective group of compounds previously isolated from the plant such as polyacetylenes seems to be responsible for its antimicrobial effect. However, ecdysteroids may also participate in the general anti-infective action of *R. carthamoides*, especially considering its antiparasitic properties.

3.7. Effect on insects

It is currently generally accepted that certain ecdysteroids play crucial roles in the control of insect growth, development, metabolism, metamorphosis, and reproduction. 20E is the principle steroid hormone in insects; however, recent data suggest that other related ecdysteroids can exert similar effects (Simonet et al., 2004). Ecdysteroids are the steroid hormones of all classes of arthropods and most likely of other invertebrates as well. The function of ecdysteroid analogues (phytoecdysteroids) in plants is still conjectural, but it is believed that they provide some degree of protection against non-adapted phytophagous insects and/or soil nematodes (Dinan, 2001). Despite the well known influence of phytoecdysteroids on insects, the effects of *R. carthamoides* on invertebrate organisms have only been partially studied. Among several researchers working in this area, Pavela (2002) reported strong repellent and antifeedant activities of ethanol extract from seeds on adults of the Colorado potato beetle (*Leptinotarsa decemlineata*). In another study published by the same author (Pavela et al., 2005), two ecdysteroid compounds, namely ajugasterone C and polypodine B decreased the fecundity of cabbage aphids (*Brevicoryne brassicae*) which fed on rape plants contaminated by water solutions of both separately tested substances. The mortality of larvae and adults significantly increased in plants treated with a specific fraction containing 20E, ajugasterone C, polypodine B and at least six other minor constituents, as well as with both individual compounds ajugasterone C and polypodine B. Although 20E has been found to be the best tolerated compound of all phytoecdysteroids tested against cabbage aphids in the study of Pavela et al. (2005), according to the results of Calas et al. (2006), 20E purified from *R. carthamoides* significantly inhibited feeding and oviposition in larvae and adults of the European grapevine moth (*Lobesia botrana*).

In addition to ecdysteroids, two lignan glycosides derived from *R. carthamoides*, namely tracheloside and carthamoside, exhibited different effects on the insects varying from high feeding deterrent activity e.g. tracheloside for the Confused flour beetle (*Tribolium confusum*) larvae, to significant feeding stimulant activity e.g. carthamoside for the Grain weevil beetle (*Sitophilus granarius*) adults in experiments performed by Harmatha and Nawrot (2002). Additionally, several sesquiterpene lactones previously detected in *R. carthamoides* appeared to be good antifeedants, with the most active substance being chlorojanerin (Cis et al., 2006).

In view of the data summarised above, the ecdysteroids are the main compounds of the plant affecting growth, development, and reproduction of insects, whilst its feeding behaviour is also significantly influenced by other groups of *R. carthamoides*-derived constituents, such as lignans and sesquiterpene lactones.

4. Toxicology

Among a number of plant species containing phytoecdysteroids, *R. carthamoides* was shown to be very safe even at high doses. In one of the earliest toxicological studies performed by Petkov et al. (1984), a root water–ethanol extract applied intraperitoneally and subcutaneously in doses up to 40 000 mg/kg did not produce mortality in male albino-mice even 7 days after its application. In the chick embryotoxicity screening test, 20E, and polypodine B isolated from roots of the plant were found not to be embryotoxic (Kosar et al., 1997). The only study showing a certain degree of toxicological risk related to *R. carthamoides* was performed by Chobot et al. (2006) on (*E*)-2-[5-(hept-5-en-1,3-diynyl)-thien-2-yl]-ethan-1,2-diol, the thiophene polyene isolated from roots of the plant. The results showed its apparent phototoxic activity, which was higher in comparison to the standard photosensitizer xanthotoxin, in histidine photo-oxidation and brine shrimp (*Artemia salina*) assays, as well as in test with sludge worms (*Tubifex tubifex*).

5. Conclusions

A great number of pharmacological and phytochemical studies carried out during last 30 years have demonstrated the vast medicinal potential of *R. carthamoides*, especially its marked adaptogenic effect. Various types of preparations, extracts and individual compounds derived from this species have been found to possess

various pharmacological effects on several organs such as the brain, blood, cardiovascular and nervous systems as well as on different biochemical processes and physiological functions including proteosynthesis, work capacity, reproduction, and sexual function, that together with some other biological actions e.g. antioxidant and immunomodulatory activities, indicates marked adaptogenic properties of the plant. Moreover, some other biological activities including anticancerogenic, antimicrobial, antiparasitic and insect antifeedant or repellent effects have been reported for extracts or individual compounds of *R. carthamoides*.

Among several classes of biologically active compounds identified in *R. carthamoides*, ecdysteroids are assumed to be its main active principle, responsible for the majority of the pharmacological effects. However, other components described in this review such as flavonoids, phenolic acids, lignans, polyacetylenes, sesquiterpene lactones, or triterpenoid glycosides may, to some degree, augment the pharmacological effects of the plant.

The data summarised above, together with the low toxicity potential of the plant, strongly support the view that the *R. carthamoides* has beneficial therapeutic properties indicating its potential as an effective adaptogenic herbal remedy. However, further studies are needed to understand the complex pharmacological action and full phytochemical profile of the plant. Clarification of the chemical composition and biological actions of the essential oil, together with verification of inconsistent results regarding reproduction and sexual function, and detailed investigation of the anticancerogenic potential or effects on insect behaviour suggest the most up-to-date challenges for the future research of *R. carthamoides*.

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