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REVIEW

Cotinus coggygria Scop.: An overview of its chemical constituents, pharmacological and toxicological potential

Sanja Matić [a,*], Snežana Stanić [a], Mirjana Mihailović [b], Desanka Bogojević [b]

[a] *Department of Biology and Ecology, Faculty of Science, University of Kragujevac, Radoja Domanovića 12, Serbia*
[b] *Department of Molecular Biology, Institute for Biological Research, University of Belgrade, Bulevar despota Stefana 142, Serbia*

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Abstract The Anacardiaceae Lindl. family comprises of many species which are used in nutrition and in traditional folk medicine for the treatment of several human diseases. *Cotinus coggygria* Scop. commonly known as "smoke tree", is a commercial ornamental plant with high medicinal usages, belongs to the family Anacardiaceae. The present review provides a comprehensive report of empirical investigations on important pharmacological activities and phytochemical screening of essential oils and extracts. Relevant information was collected from scientific journals, books, and reports via library and electronic search using Medline, PubMed, Google Scholar, ScienceDirect, Web of Science, and Scopus. The plant has been extensively investigated in a broad range of studies to provide scientific evidence for folklore claims or to find new therapeutic uses. Numerous activities namely antioxidative, antibacterial, antifungal, antiviral, anticancer, antigenotoxic, hepatoprotective and anti-inflammatory have been demonstrated for all parts of these plants by *in vivo* and *in vitro* studies. Essential oils and extracts showed various pharmacological and biological properties which make them an effective remedy for various kinds of illnesses. Considering data from the literature, it could be demonstrated that *C. coggygria* possesses diverse bioactive properties and immense utilization in medicine, health care, cosmetics and as health supplements.

* Corresponding author. Tel.: +381 34 336 223; fax: +381 34 335 040.
E-mail address: sanjamatic@kg.ac.rs (S. Matić).
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Contents

1. Introduction

Plants and natural products have been used in many parts of the world as traditional treatments for many conditions and have less deleterious side effects than corresponding synthetic drugs with the side effects which can be even more dangerous than the diseases they claim to cure. In rural areas of the developing countries, they continue to be used as the primary source of medicine (Ballabh and Chaurasia, 2007; Chitme et al., 2003).

Natural products produced as secondary metabolites by higher plants have proven to be an abundant source of biologically active compounds that can be the basis for the development of new chemicals for pharmaceuticals. Plants contain a diverse group of highly valuable and available resource of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found to have important pharmacological properties (Georgiev et al., 2014; Kashani et al., 2012; Ngule et al., 2013). In general, the plant essential oils and extracts of many plant species are considered as non-phytotoxic compounds and have been examined for a number of biological activities so far, and their antimicrobial, anti-inflammatory, antioxidant, antimutagenic, and cancer preventive effect have been partially described (Giriraju and Yunus, 2013; Kchaou et al., 2014; Matić et al., 2013).

Cotinus coggygria, also known as the ''smoke tree'', is one of the two species constituting a small genus of the family Anacardiaceae, viz., *C. coggygria* Scop. (syn.: *Rhus cotinus* L.) and *Cotinus obovatus* Raf., the American smoketree. It has a wide distribution from southern Europe, the Mediterranean, Moldova and the Caucasus to central China and the Himalayas (Novaković et al., 2007). This plant is usually either considered as large shrubs or small trees. It has glaucous, simple, ovate or obovate leaves, 3–8 cm long. The flowers are pentamerous, pale yellow or yellow–green, hermaphrodite or some of them abortive, with long peduncles, in terminal loose inflorescences (Davis et al., 1982; Tutin, 1968).

This plant has been used in folk medicine throughout the world and the medicinal properties have been investigated. *C. coggygria* is an important source of essential oils and extract with a wide range of health-promoting properties. A number of publications have reported the biological activities of extracts and essential oils from *C. coggygria* Scop. To the best of our knowledge, no study so far has been performed to summarize all the reported data on *C. coggygria* and respective biological properties. For this reason, the present review mainly focused on the botanical description, phytochemistry and pharmacological properties of extracts and essential oil from plant *C. coggygria*.

2. Botanical description and traditional uses

Anacardiaceae Lindl. is an economically important family of 82 genera and over 700 species. This family is distributed in the tropics of Africa, Asia and America with a smaller number of species occurring in subtropical and temperate areas (Wannan, 2006). Members of the family are well known for its cultivated edible fruits and seeds, dermatitis causing taxa (e.g., *Comocladia*, *Metopium*, *Semecarpus*, *Toxicodendron*), medicinal compounds, valuable timber, and lacquer plants (*Toxicodendron* and *Gluta* spp.). Many Anacardiaceae species are also valued for their horticultural appeal. Specimens of *Cotinus*, *Rhus*, *Schinus*, *Searsia*, *Pistacia chinensis Bunge*, *P. mexicana Kunth*, *Smodingium*, and *Toxicodendron* are planted for their beautiful inflorescences, infructescences, evergreen foliage, and/or fall foliage. Some of the products of Anacardiaceae, including mangos (*Mangifera indica* L. and other species), pistachios (*Pistacia vera* L.), cashews (*Anacardium occidentale* L.), and pink peppercorns (*Schinus terebinthifolia* L.), are enjoyed worldwide while other notables such as the pantropical *Spondias* and the *Neotropical* fruits are restricted to localized cultivation and consumption and are not generally transported far distances to larger markets (Pell, 2004).

Plants of the family Anacardiaceae have a long history of use by various peoples for medicinal and other purposes. Different parts of this plant have been subjected to pharmacological evaluation for their potential antiseptic, anti-inflammatory, antimicrobial, hepatoprotective (Matić et al., 2011a), antihemorrhagic agent in wound-healing (Demirci et al., 2003), as well as for countering diarrhea, paradontosis, and gastric and duodenal ulcers (Ivanova et al., 2005). There are

few reports about an internal use of ethanol infusions from the wooden parts of the plant to treat gastric ulcer and diarrhea (Ivanova et al., 2013). In Serbian folk medicine, decoction of the bark has also been used to treat cancer (Marčetić et al., 2013). The extract of *C. coggygria* is also used as a cholagogue febrifuge and for eye ailments (Li, 2009). The dried leaf and twig of *C. coggygria* is used in Chinese traditional medicine to eliminate "dampness" and "heat" and as an antipyretic (Huang, 1999). Also, *C. coggygria* syrup has the effect of protecting the liver from chemical damage, reducing tension of the choledochal sphincter, increasing bile flow and raising the body immunity (Shen et al., 1991).

Aqueous extract from the leaf of *C. coggygria* and its combinations with other extracts or agents are effective for preventing, reducing the risk and the severity of symptoms of hemorrhoids (Bruning et al., 2008). Also, a concentrated, aqueous *C. coggygria* extract can effectively induce hair growth when topically applied *in vivo* (Bruning et al., 2005).

The leaves and young branches from naturally growing trees are utilized in producing an essential oil with terpenic odor for use in perfumery in various countries (Demirci et al., 2003; Tsankova et al., 1993).

The roots are used in the dying of leather and cloths into a yellowish color (Baytop, 1999; Tsankova et al., 1993). The heartwood of the plant is gold-like and shining, and contains a yellow dye that has been used for dying leather and cloth (Arampatzis, 2001).

3. Phytochemical studies

A large number of compounds have been identified and isolated from various parts of the *C. coggygria* plant (summarized

Table 1 *Cotinus coggygria* extracts and their main compounds.

Solvents used	Plant part used	Main compounds	References
Ethanol	Branches	1,2,3,4,6-Penta-O-galloyl-β-D-glucose	Cha et al. (2009)
Methanol	Heartwood	Sulfuretin	Valianou et al. (2009)
		Fisetin	
		Dustin	
		Quercetin	
		Taxifolin	
		Butin	
Methanol	Flowers leaves	Gallic acid	Šavikin et al. (2009)
Crude extract	Heartwood	3′,4′,7-Trihydroxyflavanone	Antal et al. (2010)
Ethyl acetate	Whole plants	Disulfuretin	Westenburg et al. (2000)
Methanol	Stem	Myricetin	Matić et al. (2013)
Ethyl-acetate	Shoots	Gallic acid	Simić et al. (2008)
Acetone	Shoots	Gallic acid	Marčetić et al. (2013)

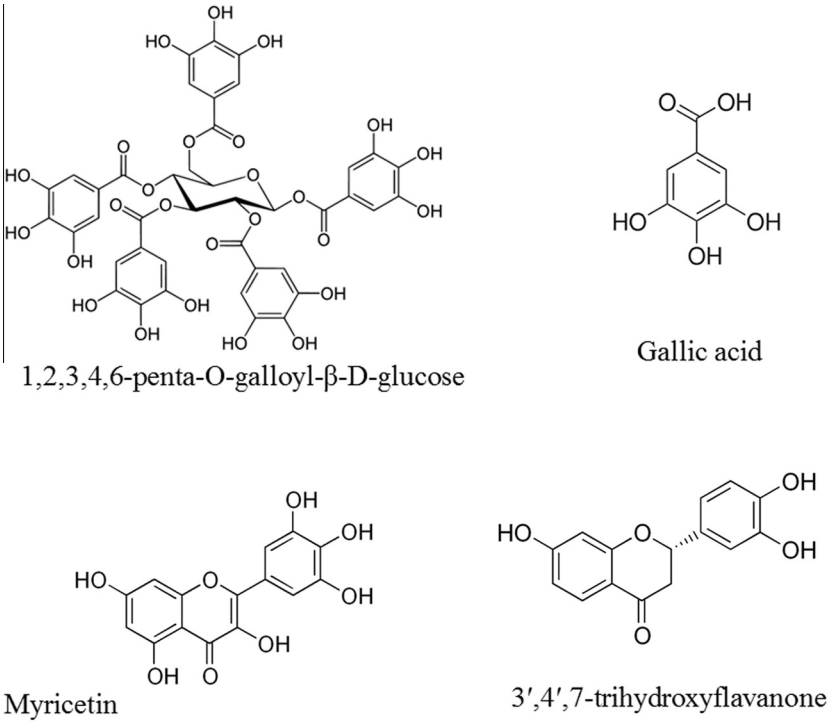

Figure 1 Chemical structures of some bioactive compounds identified and isolated from various parts of the *Cotinus coggygria* plant.

Table 2 Total phenolic, flavonoids and tannins contents of various parts of *Cotinus coggygria*.

Solvents used	Part used	Total phenols	Flavonoids	Tannins	References
Ethyl-acetate	Shoots	92.9%	3.5%	83.4%	Simić et al. (2008)
Methanol	Flowers	/	76.5 GA/g	13.7 GA/g	Šavikin et al. (2009)
	Leaves		515.5 GA/g	18.5 GA/g	
Methanol	Stem	3.78 GA/g	8.2 R/g	/	Matić et al. (2013)

GA/g – gallic acid per gram of dry weight of plant.
R/g – rutin per gram of dry weight of plant.

in Table 1). The structures of some of these compounds are presented in Fig. 1.

The phytochemical investigation of the ethanol extract of the branches of *C. coggygria* resulted in the isolation of 1,2,3,4,6-penta-O-galloyl-β-D-glucose, together with two related components 1,2,3,6-tetra-O-galloyl-β-D-glucose and gallic acid (Cha et al., 2009).

Phytochemical analysis of the *C. coggygria* methanol extract of the heartwood, performed by Valianou et al. (2009) indicated the presence of 3′,4′,6-trihydroxyaurone (sulfuretin), 3′,4′,7-trihydroxyflavonol (fisetin), 3′,4′,7-trihydroxy flavanol (fustin), 3′,4′,5,7-tetrahydroxyflavonol (quercetin), 3′, 4′,5,7-tetrahydroxyflavanol (taxifolin), 4′,7-dihydroxyflavanol, 3′,4′,7-trihydroxyflavanone (butin), 4′,7-dihydroxyflavanone (liquiritigenin), trans-2′,3,4,4′-tetrahydroxychalcone (butein), 4′,5,7-trihydroxyflavanone, and trans-2′,4,4′-trihydroxychal cone (isoliquiritigenin).

Total phenols, flavonoids and tannins are the main group of biologically active constituents in ethyl-acetate and methanol extracts of various parts of *C. coggygria* (Table 2). According to HPLC profiles, gallic acid and its derivatives were the dominant in flowers and leaves of the *C. coggygria* extracts (Šavikin et al., 2009).

Phytochemical investigations of *C. coggygria* wood resulted in the isolation of the novel C-3/C-3″ dimer of butin (3′,4′,7-tri hydroxyflavanone) and other known compounds: gallic acid and its methyl ester; catechin; profisetinidins: fisetinidol-(4α → 8)-(+)-catechin and epifisetinidol-(4β→8)-(+)-cate chin; flavanonols: fustin and dihydroquercetagetin; flavanones: butin and eriodictyol; flavonols: fisetin and quercetin; the chalcone butein and the aurone sulfuretin (Antal et al., 2010).

Westenburg et al. (2000) reported six compounds in the ethyl acetate partition of the whole plant of *C. coggygria*, namely, disulfuretin {2,2'-[1,2-bis(3,4-dihydroxyphenyl)-1,2-et hanedylidene]-bis[6-hydroxy-3(2H)-benzofuranone], sulfuretin, sulfurein, gallic acid, methyl gallate, and pentagalloyl glucose.

Methanol extract from the stem of *C. coggygria* contained 3.78 mg gallic acid per gram of dry plant material in total phenolics, while the content of flavonoids was 8.29 mg rutin per gram of dry plant material (Table 2). HPLC analysis showed that myricetin was a major component in the extract (511.5 μg/g). Also, hydroxylderivatives of cinnamic acids (chlorogenic, caffeic, coumaric, ferulic, and rosmaric acid) were identified in the extract in various amounts. Rosmaric acid (18.55 μg/g) was the major phenolic acid in the extract, while the other phenolic acids were present in lower amounts (Matić et al., 2013).

Highest content of total phenolics (92.9%), tannins (83.4%) and flavonoids (3.5%) was determined in ethyl-acetate fraction from ground, dried young shoots in comparison to chloroform and water fractions. In this fraction gallic acid, apigenin, luteolin and their derivatives were detected by HPLC (Simić et al., 2008).

The acetone extract from young shoots of *C. coggygria* is characterized by the presence of the gallic acid, gallic acid derivatives and flavonol kaempferol-3-O-glucoside. In the ethyl acetate fraction, gallic acid, gallic acid derivatives, kaempferol-3-O-glucoside and the flavones luteolin-7-O-glucoside, luteolin-8C-glucoside (orientin), apigenin glycoside and apigenin were detected (Marčetić et al., 2013).

Riaz et al. (2012)performed the phytochemical screening on the *n*-hexane, chloroform, ethyl acetate, *n*-butanol and aqueous fractions and showed presence of the phenolic, cardiac glycosides and flavonoids in large amounts in the chloroform, *n*-butanol and ethyl acetate soluble fraction. Flavonoids and phenolic were found in more amounts in ethyl acetate than in chloroform and *n*-butanol fractions, while in very less amounts in aqueous and *n*-hexane fractions. Cardiac glycosides were found in more amounts in the ethyl acetate, chloroform and *n*-butanol fractions while in less amount in other two fractions. Alkaloids were found in maximum concentration in the ethyl acetate fraction as comparative to other fractions whereas absent in the aqueous fraction. Terpenoides and saponins were found in all fractions but saponins were very less in *n*-hexane and chloroform fraction. Tannins and sugars were found in all the polar fractions whereas absent in *n*-hexane soluble fraction. Sugars were found in more amounts in the remaining aqueous fraction.

Thirty-eight components from group of monoterpenes and sesquiterpenes were characterized in the essential oils from the flowers of *C. coggygria* from the south Serbia, forty-three components in oil from the leaves and twenty-five components in oil from the stems. The main constituents in the essential oils of flowers, leaves and stems were the monoterpenes limonene (39.5%, 6.5% and 3.39%) and α-pinene (16.0%, 15.1% and 21.9%), respectively (Milošević et al., 2008).

Analyses of two essential oils, both obtained from the leaves with young twigs of wild-growing *C. coggygria* from two localities in Serbia (Deliblatska peščara and Zemun), showed very similar chemical composition with monoterpenic hydrocarbons dominating (87.4% and 93.1%, respectively) The major components, i.e. limonene (47.0% and 39.2%), (Z)-β-ocimene (16.4% and 26.3%), α-pinene (8.2% and 8.4%), (E)-β-ocimene (4.6% and 9.0%) and terpinolene (6.8% and 5.3%) were the same in both oils (Novaković et al., 2007).

In the oils from Turkey the main constituents were limonene 48.5%, (Z)-β-ocimene 27.9% and (E)-β-ocimene 9.7% (Demirci et al., 2003). In the oils from Bulgaria the main components were α-pinene 44.0%, limonene 20.0%, β-pinene 11.4% (Tsankova et al., 1993). In the oils from Hungary the

main constituents were limonene 30.0–40.0%, α-pinene 24.4–34.3%, β-pinene 7.6–20.2%, Δ3-carene 4.6–11.0%, and α-terpinolene 3.3–10.6% (Hethelyi et al., 1986). In the oils from Greece the main components were different in different samples: in the first oil, the main constituents were limonene 67.4%, α-pinene 14.7%, and terpinolene 8.6%; in the second, myrcene 32.0%, sabinene 18.0%, and α-pinene 15.9%; in the third oil, main components were sabinene 24.2%, myrcene 14.0%, limonene 10.9% and terpin-4-ol 10.9% (Tzakou et al., 2005).

4. Pharmacological activities

4.1. Antioxidant activity

The antioxidant activity of extracts and essential oil is a biological property of great interest because they may preserve foods from the toxic effects of oxidants (Maestri et al., 2006).

Matić et al. (2011a) examined the reducing power, ferrous chelating and the free-radical-scavenging activities of the methanol extract from the stem of the plant *C. coggygria*. Results showed that the reducing power of the extract increased in a concentration-dependent manner and was consistently greater than that of cysteine, which was used as the standard. At 60 μg/ml, the extract exhibited an almost twofold higher reducing power than cysteine. The ferrous chelating activity of the *C. coggygria* extract increased with increasing concentration up to 20 μg/ml at which concentration the extract possessed a 78% chelating effect. The free-radical-scavenging activity of the methanolic extract was quantitatively determined with the DPPH radical-scavenging assay. The maximum inhibiting effect of the extract on DPPH radicals was about 95%, while the maximum inhibitory concentration is approximately 125 μg/ml.

Šavikin et al. (2009) reported that the methanol extracts of leaves and flowers of *C. coggygria* showed strong antioxidant activity in reaction with DPPH (IC_{50} = 2.6 ± 0.4 and 3.8 ± 0.5 μg/ml, respectively) and an inhibition of lipid peroxidation.

Chloroform, ethyl-acetate and water fractions from ground, dried young shoots showed antioxidant effects but the highest activity was obtained with the ethyl-acetate fraction (Simić et al., 2008). This fraction also exhibited significant ferric reducing ability (5.0 mmol Fe^{2+}/g extract), very high DPPH radical scavenging activity (SC_{50} = 1.7 μg/ml) and high inhibition of lipid peroxidation on liposomes (IC_{50} = 41.8 μg/ml).

Similar results for ethyl acetate fraction were observed in a study by Riaz et al. (2012). Ethyl acetate fraction showed highest % inhibition of the DPPH radical when compared with the other fractions i.e. 81.64 ± 1.29% inhibition of the DPPH radical at the concentration of 30 μg/ml. Its IC_{50} value was found to be 15.58 ± 0.09 μg/ml, comparative to the butylated hydroxytoluene (BHT), which has IC_{50} value of 12.6 ± 0.85 μg/ml. Values of IC_{50} shown by *n*-hexane fraction, chloroform fraction, ethyl acetate fraction, *n*-butanol fraction and aqueous fraction were 147.29 ± 1.18, 52.30 ± 0.43, 58.32 ± 0.71, and 59.58 ± 0.84 μg/ml, respectively. Ethyl acetate fraction also showed the highest lipid peroxidation inhibition (61.41 ± 1.16%), as well as highest values of ferric reducing antioxidant power (697.76 ± 1.98 μg of trolox equivalents), and total antioxidant activity (1.02 ± 0.09) comparative to the other studied fractions.

Matić et al. (2011a) examined the *in vivo* potential of the methanol extract of the plant *C. coggygria* to counteract oxidative stress induced in Wistar rats by the intraperitoneally administration of hepatotoxic compound pyrogallol measuring the level of TBARS and activities of antioxidant enzymes. One hour after treatment with pyrogallol, the serum and liver levels of TBARS was 1.81- and 3.23-fold, respectively, above the basal value measured in the negative control. Administration of the extract prior to the pyrogallol treatment attenuated the rise in TBARS. Treatment with the extract 12 h prior to pyrogallol was slightly more effective than the 2 h pretreatment, while administration of the extract alone did not induce a rise in liver and serum TBARS levels. Pyrogallol administration caused a decline of the total liver SOD activity to 71.38% of the basal value which was assumed to be 100%. In animals pretreated with the *C. coggygria* extract 2 and 12 h before pyrogallol administration, the total SOD activity was 88.62 and unchanged at 96.51% of the basal value, respectively. Also, a comparable effect on MnSOD and CuZnSOD activity was observed. While pyrogallol administration induced a pronounced decline in CAT activity to 31.80% of the basal level, after the 2 and 12 h pretreatment with the extract this activity was 47.54% and 81.64% of basal CAT activity, respectively. Pyrogallol induced a decline in GST activity to 80.45%, while the 2 and 12 h pretreatment alleviated this decrease, allowing for 91.56% and 98.71% of the basal enzymatic activities, respectively.

In a recent study, Yarat et al. (2013) have evaluated the *in vitro* effect of *C. coggygria* aqueous extract on glutathione level (GSH) and superoxide dismutase activity in saliva samples obtained from clinically healthy subjects. According to findings, the GSH levels of saliva samples incubated with *C. coggygria* were significantly higher than those of untreated saliva samples, while the SOD activity were significantly lower than untreated samples.

4.2. Anticancer activity

Due to the limitations of surgery and radiotherapy and the side effects of chemotherapy as cancer therapy, there is increasing interest in developing antitumor drugs from natural products.

Methanol extracts of leaves and flowers of *C. coggygria* exhibited significant cytotoxic effects toward human cervix carcinoma HeLa cells and human colon carcinoma LS174 cells. Results showed that extracts of leaves and flowers possessed potential cytotoxic activity toward HeLa cells with an IC_{50} values of 19.01 ± 3.9 and 29.4 ± 3.5 μg/ml, respectively, and against LS174 human cancer cell lines with an IC_{50} of 65.4 ± 12.3 and 41.3 ± 3.9 μg/ml, respectively (Šavikin et al., 2009).

Marčetić et al. (2013) showed that the ethyl acetate fraction of the acetone extract of young shoots of *C. coggygria* exerted a strong dosedependent cytotoxic activity on HeLa cells. The cytotoxic effect of the ethyl acetate fraction was more pronounced (IC_{50} = 15.6 ± 0.8 μg/ml) than the activity of tannin (IC_{50} = 17.3 ± 6.9 μg/ml), but weaker than the cytotoxicity of gallic acid (IC_{50} = 10.0 ± 0.5 μg/ml).

The potential cytotoxic effect of hexane, ethanol and water extracts from *C. coggygria* on two eukaryotic cell lines, human

gingival fibroblasts (HGF-1) and keratinocyte (HaCaT), was assessed using XTT (Cell Proliferation Kit II) assay (Ferrazzano et al., 2013). Water extract from *C. coggygria* were slightly, but measurably, affect the viability of both cell lines ($p < 0.001$), while the ethanolic extract appeared to be toxic to both cell lines ($p < 0.0001$).

4.3. Antigenotoxic activity

The genotoxicity of a methanol extract from stem of *C. coggygria* was examined using short tests for the detection of mutagenicity under *in vivo* conditions, i.e. the sex-linked recessive lethal (SLRL) test and alkaline comet assay. The SLRL test revealed the genotoxic effect of the 5% methanol extract on the eukaryotic model system *Drosophila melanogaster* in premeiotic germinative cell lines, i.e. spermatozoids, as well as spermatocytes, while spermatids proved to be more resistant to the genotoxic effects of the extract (Matić et al., 2011b). The comet assay was carried out on rat liver and bone marrow at 24 and 72 h after intraperitoneal administration of extract in concentrations of 500, 1000 and 2000 mg/kg body weight. Comet tail moment and total scores in the group treated with 500 mg/kg body weight, 24 and 72 h after treatment were not significantly different from the control group. Under the same circumstances, in the groups treated with 1000 and 2000 mg/kg body weight of the extract there was a significant increase in damages when compared to the control group.

In addition, Matić et al. (2013) reported no significant increase in tail moment in liver at 2, 12, 24, 48, and 72 h after treatment with 500 mg/kg body weight of the extract compared with the negative control group. Statistically significant enhancement in tail moment was seen in groups of animals at all time intervals after treatment with 1000 and 2000 mg/kg body weight.

The antigenotoxic effects of *C. coggygria* methanol extract was investigated using the Drosophila sex-linked recessive lethal test and comet assay. Post-treatments with methanol extract in concentration of 2% drastically reduced the frequency of sex-linked recessive lethal mutations induced by 0.75 ppm of EMS in two germ cell lines (spermatozoides and spermatides) with high significance ($p < 0.5^{*}$, $p < 0.001^{***}$) toward the positive control (Stanić et al., 2011). The alkaline comet assay was performed to assess whether pretreatment with 500 mg/kg body weight of the *C. coggygria* extract can improve DNA damage in liver resulting from pyrogallol administration. Although pyrogallol caused a statistically significant increase in comet tail length, percentage of DNA in the tail and tail moment compared with the negative control group, pre-treatments with the extract 2 or 12 h prior to pyrogallol administration resulted in a statistically significant decrease in selected comet parameters. The percentage reduction in the total comet score (%R) was more pronounced in the group of rats exposed to pyrogallol 12 h after treatment with extract (86.1%) and less strong (69.4%) for the group of rats exposed to pyrogallol 2 h after pretreatment with the extract (Matić et al., 2011a, 2013).

4.4. Antimicrobial activity

Plants produce various chemical components of different biological activities including antimicrobial that were shown to have active effect against various microorganisms. A number of studies have demonstrated the antimicrobial properties of *C. coggygria* extract against a wide range of microorganisms (Table 3).

The *in vitro* antimicrobial activity of the methanol extract of *C. coggygria* was examined on five different bacterial species namely *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Micrococcus lysodeikticus*, and yeast *Candida albicans* using the cylinder plate and macro broth dilution method (Matić et al., 2011c). The highest concentration of the methanol extract (500 μg) was active against all examined bacteria with the inhibition zones ranging from 9 to 18 mm. Very sensitive bacteria toward methanol extract are *E. coli* (in amounts of 150 and 300 μg inhibition zones are 29 and 17 mm, respectively) and *M. lysodeikticus* (150 and 300 μg of extracts produced inhibition zones of 20 and 18 mm, respectively). All phytopathogenic bacteria were sensitive in the presence of the extract in an amount of 300 to 500 μg, while *C. albicans* was resistant. According to IC values, the tested extract shows antibacterial activity between 125 and 250 μg/ml against all tested pathogenic bacteria. Although the MICs obtained with the methanol extracts are high compared with those of Amracine, in general between 125 and 250 μg/ml (Matić et al., 2011c).

Methanolic leaf extract of *C. coggygria* were tested against seven bacterial strains (*B. subtilis*, *S. aureus*, *E. coli*, *Enterobacter aerogenes*, *K. pneumoniae*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*) by disk diffusion method. *C. coggygria* extract in concentration of 10 μg/ml, 20 μg/ml, and 1 g/ml showed moderate effect on all the bacterial strain (Singh et al., 2012).

Previous study was reported the antimicrobial activity of *C. coggygria* ethanol extract (Borchardt et al., 2008). Leaf extracts of *C. coggygria* inhibited *S. aureus* and *P. aeruginosa* whit inhibition zones of 13 and 10 mm. Although *C. albicans* and *E. coli* were included in this study inhibition of these microorganisms was not reported.

The antibacterial activity of *C. coggygria* leaves extracts, which grows naturally in Turkey, prepared with various solvents, were determined by disk diffusion method. The extract in distilled water were found to be most effective against *Enterococcus faecalis*, with an inhibition diameter of 20 mm, while methanol extract were observed to be most effective against *S. aureus*, *S. epidermidis* and *E. faecalis* (Tunç et al., 2013).

The antimicrobial activity, expressed as the minimum inhibitory concentration (MIC) of the acetone extract and the fractions obtained from young shoots of *C. coggygria* were in the range of 3.1 to 200 mg/ml (Marčetić et al., 2013). The acetone extract inhibited the growth of the Gram-positive bacteria *S. epidermidis* (MIC = 25 mg/ml) and *S. aureus* (MIC = 25 mg/ml), whereas the ethyl acetate fraction was active against *B. subtilis* (MIC = 25 mg/ml), *K. pneumoniae* (MIC = 50 mg/ml) and *E. coli* (MIC = 50 mg/ml). The highest activity was obtained with the chloroform fraction on the yeast *C. albicans* (MIC = 3.1 mg/ml) more effectively than the control antifungal drug nystatin (6.2 mg/ml).

The agar well-diffusion method was used to evaluate the activity of hexane, ethanol and water extracts from *C. coggygria* in concentration of 12.5, 25 and 50 mg/ml against *Streptococcus mutans*, *Streptococcus sobrinus*, *Lactobacillus casei*, and *Actinomyces viscosus*. The water and ethanolic

Table 3 Antimicrobial activity of *Cotinus coggygria* Scop. extract.

Plant extract	Plant part tested	Method	Microorganism	MIC[a] or inhibition zone[b]	References
Methanol	Stem	Cylinder plate and macro broth dilution	*S. aureus*	250[a]	Matić et al. (2011c)
			B. subtilis	125[a]	
			K. pneumonia	250[a]	
			E. coli	250[a]	
			M. lysodeikticus	250[a]	
			C. albicans	125[a]	
Ethanol	Leaves	Disk diffusion	*S. aureus*	13[b]	
			Pseudomonas aeruginosa	10[b]	
Water	Leaves	Disk diffusion	*E. faecalis*	20[b]	Tunç et al. (2013)
				19[b]	
Methanol			*S. aureus*	17[b]	
			S. epidermidis	14[b]	
Acetone	Shoots	Broth microdilution	*S. epidermidis*	25[a]	Marčetić et al. (2013)
			S. aureus	25[a]	
Ethyl acetate			*B. subtilis*	25[a]	
			K. pneumoniae	50[a]	
			E. coli	50[a]	
Chloroform			*C. albicans*	3.1[a]	
Water	Whole plant	Agar well-diffusion	*Streptococcus mutans*	10[b]	Ferrazzano et al. (2013)
			S. sobrinus	16[b]	
			Actinomyces viscosus	11[b]	
			Lactobacillus casei	16.8[b]	
Hexane			*S. sobrinus*	11.8[b]	
			S. sobrinus	9.3[b]	
Ethanol			*S. mutans*	10.1[b]	
			A. viscosus	9.3[b]	

[a] MIC; minimum inhibitory concentration.
[b] Inhibition zone.

extracts of *C. coggygria* demonstrated a considerable activity against all the four bacteria at any concentration tested (Ferrazzano et al., 2013).

Essential oils from leaves with young branches of *C. coggygria* from two localities in Serbia (Deliblatska peščara and Zemun), were tested for antibacterial and antifungal activities (Novaković et al., 2007). The essential oil from Deliblatska peščara showed inhibition zones from 6 to 23 mm. The highest zones were obtained against the *Staphylococcus* and *Micrococcus* species, while the lowest activity was against *Proteus mirabilis*. Inhibition zones of 6–28 mm were obtained for the oil from Zemun, with slightly higher activity against *Staphylococcus* species than of the oil from Deliblatska peščara. Both oils showed higher antibacterial activity than streptomycin used as the positive control, except in the case of *P. mirabilis*. The oil from Deliblatska peščara showed lower antibacterial activity in this test with bacteriostatic activity in the concentration range 2.5–5.0 µl/ml, while bactericidal concentrations were in the range of 2.5–10.0 µl/ml. The essential oil from Zemun showed activity with MIC and minimum bactericidal concentration (MBC) values ranging from 1.25 to 5.0 µl/ml. The oil from Deliblatska peščara showed antifungal activity with MIC values of 5.0–40.0 µl/ml and MFC values of 10.0–40.0 µl/ml. The antifungal activity of the oil from Zemun was even better with MIC values between 1.25 and 10.0 µl/ml and minimum fungicidal concentration (MFC) values of 2.5–20.0 µl/ml. *Trichoderma viride* showed higher resistance to both oils, while *C. albicans* and *Trichophyton mentagrophytes* were more sensitive than the other fungi. The commercial fungicide, bifonazole, used as the positive control showed activity with higher MIC and MFC values than the essential oils.

The agar diffusion method was used to evaluate effects of the essential oils from flowers, leaves and stems of *C. coggygria* against one fungi and six bacterial species (Milošević et al., 2008). The essential oil from the stems showed maximal inhibition zones against *S. aureus* (35 mm), while significant the inhibition zone diameter was observed for pure oils of flowers and leaves against *K. pneumoniae* (34 and 30 mm, respectively).

4.5. Antiviral activity

Plants are rich sources of bioactive constituents with insecticidal, fungicidal and antiviral activity. Reports of natural antiviral compounds, mainly from plants, has increased immensely

during the last decade (Chen et al., 2004; Fan et al., 2005; Ma et al., 2007).

There are two main modes of action of antiviral agents: one is inhibition of infection, and the other is the inhibition of viral replication. The activity of *C. coggygria* extract on infection and replication was determined by local lesion and leaf-disk methods (Jing et al., 2012). Ethanol extract from leaves of *C. coggygria* showed particularly strong inhibitory activity against Tobacco mosaic virus (TMV) infection (93.52%) and greatly inhibited viral replication (38.17%).

4.6. Hepatoprotective activity

In a recent study, Pavlov and coworkers (2013) investigated the toxicity of *C. coggygria* leaves aqueous infusion in male Wistar rats. Animals were treated by stomach gavage with herb infusion in concentrations of 1%, 2% and 4%. Results showed that treatment with aqueous infusion did not reveal subchronic toxicity on liver. Histological investigation did not detect pathological deviations in the liver of treated groups, also no significant changes were observed in the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP).

According to Ivanova et al. (2013) the biochemical measurements did not reveal any toxicity in the liver in group treated by stomach gavage with the 20% ethanol infusion from *C. coggygria* wood. The estimated values of serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase (128 ± 12.24, 28.89 ± 1.74, and 356.4 ± 31.17, respectively) when compared with the negative control group (120.2 ± 13.21, 31.33 ± 2.84, 408 ± 53.43, respectively) suggested that liver function is not affected. In addition, histological investigation did not detect pathological deviations in liver of treated group compared with controls. Also, a significant decrease in the number of apoptotic cells in the liver was detected in the group treated with 20% ethanol infusion.

A recent study examined the hepatoprotective potential of the *C. coggygria* methanol extract in Wistar rats treated with the pyrogallol, an inducer of acute liver damage (Matić et al., 2013). The methanolic extract at a dose of 500 mg/kg body weight was applied either 2 or 12 h prior to administration of 100 mg/kg body weight of pyrogallol. Although the treatment with pyrogallol produced a significant increase in the serum AST, ALT, ALP levels and in total bilirubin, the methanol extract of *C. coggygria* significantly reduced pyrogallol-induced elevation in the serum enzymes and in total bilirubin. Also, the extract alone did not produce significant alterations in the serum enzymes compared with control group.

Matić et al. (2011a, 2013) examined the expression of hepatic haptoglobin (Hp), α_2-macroglobulin (α_2M), Nuclear Factor-KappaB (NF-κB), serine–threonine kinase Akt, and the signal transducer and activator of transcription 3 (STAT3) after *C. coggygria* extract administration. The highest levels of α_2M and Hp were detected 12 and 24 h after extract administration. When the *C. coggygria* extract was administrated 2 and 12 h before pyrogallol, increased levels of Hp and α_2M were detected 12 h before pyrogallol administration. Pyrogallol administration induced NF-κB protein expression and significant activation, while administrations of the *C. coggygria* extract 2 or 12 h before the pyrogallol treatment effectively prevented the increase of NF-κB. Although pyrogallol treatment promoted a reduction of Akt activity, administration of the *C. coggygria* extract, either 2 or 12 h before the pyrogallol treatment causes a increase in the levels of active Akt kinase. While pyrogallol administration induced a slight reduction of STAT3 activity in whole-liver homogenates, treatment with *C. coggygria* extract either 2 or 12 h before the pyrogallol treatment increased the levels of STAT3. The *C. coggygria* methanol extract alone induced STAT3 protein expression and activation.

4.7. Anti-inflammatory activity

In a recent study, the ethyl-acetate fraction from dried young shoots of the *C. coggygria* was screened for its possible anti-inflammatory activity on carrageenan induced edema in rat paw at doses of 50 and 100 mg/kg. The fraction showed significant ($p < 0.01$) anti-inflammatory activity in a dose-dependent manner. Doses of 50 and 100 mg/kg led to a 46.5% and 76.7% reduction of the edema, respectively (Marčetić et al., 2013). Also, dose of the 100 mg/kg was more pronounced than the activity of the anti-inflammatory drug indomethacin (53.8%).

Matić and coworkers (2011a) examined induction of the acute phase response that is characterizated by liver production of a set of acute phase proteins after a single intraperitoneally dose of *C. coggygria* methanol extract. The concentrations of Hp and α_2M, were determined by rocket immunoelectrophoresis with anti-human Hp and α_2M antibodies. In this study, extract administration promoted the highest increase in acute phase reactants Hp and α_2M 24 h after *C. coggygria* extract. The level of the examined acute phase proteins returned to the basal level 72 h after treatment with the extract. Also, the relative concentrations of Hp and α_2M were lower than those during the acute phase response observed after treatment with turpentine.

4.8. Other activities

Antal et al. (2008) reported the first *in vivo* results demonstrating the elevation of cerebral acetylcholine level by an auroneenriched *C. coggygria* fraction. In this study the methanol extract from the heartwood of *C. coggygria* were shown to inhibit acetylcholinesterase (AChE) with an IC_{50} of 89.3 μg/ml and $CI_{95\%}$ ranging from 72.4 to 108.7 μg/ml.

The ethanol extract of the branches of *C. coggygria* exhibited a significant *in vitro* inhibition on the yeast α-glucosidase, one of the key enzymes related with diabetes mellitus, in a dose dependent manner. Its major compound 1,2,3,4,6-penta-O-galloyl-β-D-glucose demonstrated a strong inhibition on the yeast α-glucosidase *in vitro* with an IC_{50} of 0.96 mg/ml (Cha et al., 2009).

Yarat et al. (2013) have evaluated the *in vitro* effectiveness of *C. coggygria* aqueous extract on tissue factor activity in saliva samples obtained from clinically healthy subjects. According to findings, *C. coggygria* extract caused an increase in salivary buffering capacity, decrease number of bacteria and prevented bacterial aggregation.

The possible immunostimulant effects of the methanolic extract of *C. coggygria* and its protection against pathogenic bacteria *Vibrio anguillarum* in cultured koi carp (*Cyprinus*

carpio carpio) were reported by Bilen et al. (2013). Groups of koi fed diets supplemented with extract had less mortality following challenge infection with *V. anguillarum* compared with groups of koi fed extract-free diets.

Furthermore, the results of a recent study by Pavlov et al. (2013) described the effect of aqueous infusion from *C. coggygria* leaves on indomethacin-induced gastric mucosal damage in Wistar rats and its possible effect on the gastric oxidative status. Morphometrically examinations of stomachs showed that the aqueous infusion significantly decreased the ulcer number and area, while histopathological studies demonstrated that this infusion induced a reduction of the depth and severity of indomethacin-induced mucosal lesions. Also, aqueous infusion from *C. coggygria* reduced the indomethacin-induced elevation of gastric malondialdehyde (MDA), ALP and uric acid (UA) levels.

5. Conclusions

Essential oils and extracts obtained from many plants have recently gained a great popularity and scientific interest. *C. coggygria* is an important source of essential oils and extract with a wide range of biological activities such as antibacterial, antifungal, antiviral, anticancer, antigenotoxic, hepatoprotective and anti-inflammatory. In traditional and folklore medicine, it has been used for its many pharmacological and biological activities, which make it an effective remedy for various kinds of illnesses. Considering data from the literature, it could be demonstrated that *C. coggygria* possesses diverse bioactive properties and immense utilization in medicine, health care, cosmetics and as health supplements.

Conflict of interest

The authors declare that there are no conflicts of interest for the information presented in this review.

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