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Promising Cytotoxic Activity Profile, Biological Activities and Phytochemical Screening of *Verbascum* L. Species

Cigdem Kahraman[1] • Zeliha S. Akdemir[1] • I. Irem Tatli[2*]

[1] Department of Pharmacognosy, Faculty of Pharmacy, Hacettepe University, TR-06100 Ankara, Turkey
[2] Department of Pharmaceutical Botany, Faculty of Pharmacy, Hacettepe University, TR-06100 Ankara, Turkey

Corresponding author: * itatli@hacettepe.edu.tr

ABSTRACT

Verbascum species, the largest genus of the family Scrophulariaceae, have been used in traditional medicines for centuries in almost all parts of the world. In this paper, the usage, biological activities (antioxidant, anticholinesterase, antiinflammatory, antinociceptive, wound healing, cytotoxic, anticancer, antitumor, immunomodulatory, antimicrobial, antimalarial, anthelmintic, antiviral, antitussive, anti-ulserogenic, hepatoprotective, antihyperlipidemic, pesticidal, antigermination and the other activities), chemical constituents of these species and new species of the genus are reviewed.

Keywords: Scrophulariaceae, secondary metabolites

Abbreviations: **AChE**, acetylcholinesterase; **ALT**, alanine aminotransferase; **ALP**, alkaline phosphatase; **AST**, aspartate aminotransferase; **ATCC**, American Type Culture Collection; **BChE**, butyrylcholinesterase; **BT-549**, Ductal carcinoma cell; **CCl_4**, carbon tetrachloride; **DPPH**, 2,2-diphenyl-1-picrylhidrazyl; **ELISA**, Enzyme-Linked ImmunoSorbent Assay; **FRAP**, ferric-reducing antioxidant power; **FVI**, the lyophilized infusion from the flowers of *V. thapsiforme*; **Hep-2**, Larynx carcinoma cell; **HepG2/C3**, Hepatic carcinoma cells; **HL-60**, Human promyelocytic leukemia cells; **HSV-1**, Herpes simplex virus type 1; **IC_{50}**, Half maximal inhibitory concentration; **iNOS**, Inductible Nitric Oxide Synthase; **KB**, Epidermoid carcinoma; **LFA-1/ICAM-1**, Leukocyte function-associated antigen-1/Intracellular adhesion molecule-1; **MCF-7**, Human breast adenocarcinoma cell; **MDCK**, Madin-Darby Canine Kidney Cells; **MIC**, Minimum inhibitory concentration; **MTT**, 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide; **NHED**, Naturopathic Herbal Extract Ear Drops; **PGE1**, Prostaglandin E1; **PGE2**, Prostaglandin E2; **RAPD**, Random amplification of polymorphic DNA; **SK-MEL**, Malignant melanoma cell; **SK-OV-3**, Ovary carcinoma cell; **TLC**, Thin Layer Chromatography; **TPA**, 12-*O*-tetradecanoyl-13-acetate; **XTT**, 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide

CONTENTS

INTRODUCTION

The genus *Verbascum*, commonly known as "mullein", is a widespread genus of the family Scrophulariaceae, which comprises more than 2500 species worldwide. The genus is represented by 233 species, 196 of which are endemic in Turkish Flora (Huber-Morath 1978; Davis *et al*. 1988; Ekim 2000). Various preparations of some species of this genus

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Invited Review

have been used as expectorant and mucolytic, as well as sedative, diuretic and constipate in traditional Turkish medicine. Mullein has also been used for the respiratory disorders such as bronchitis, dry coughs, tuberculosis and asthma in traditional Turkish medicine. *Verbascum* species are used to treat hemorrhoids, rheumatic pain, superficial fungal infections, wounds and diarrhea, and have inhibitory activities against the murine lymphocytic leukemia and influenza viruses A2 and B. The oil made from the flowers is used to help soothe earache and can be applied externally for eczema and other types of inflammatory skin conditions. They are traditionally consumed as a tea to relieve abdominal pains. A decoction of roots febrifuge is used to alleviate toothache and also to relieve cramps, convulsions and migraines. The leaves, roots and the flowers are also anodyne, antiseptic, antispasmodic, astringent, emollient, nervine, vulnerary, analgesic, antihistaminic, anticancer, antioxidant, antiviral, bactericide, cardiodepressant, oestrogenic, fungicide, hypnotic and sedative. In addition to the abovementioned common uses, these species have been used for pruritic conditions in urogenital organs (Baytop 1999; Turker and Camper 2002; Turker and Gurel 2005). *Verbascum* species contain biologically active compounds, such as flavonoids, phenylethanoid and neolignan glycosides, saponins, iridoid glycosides (Tatli and Akdemir 2004). In addition, the commercial popularity of *Verbascum* species has been increasing for the past few years with the growing interest in herbs and preference for the 'greener' lifestyle. Today in health food stores in the United States, one can easily find dried leaves and flowers, swallow capsules, alcohol extracts and flower oil of mullein (Baytop 1999; Turker and Camper 2002; Turker and Gurel 2005).

Plants have been used as folkloric sources of medicinal agents since the beginning of mankind. As the age of modern medicine, plant-derived active principles, their semi-synthetic and synthetic analogs have served as a major route to new pharmaceuticals. In particular, since 1961, plant-derived compounds have been approved for use as anticancer drugs: vinblastin (Velban®), vincristin (Oncovin®), etoposide (VP-16®), taxol (Paclitaxel®), etc. (Lee 1999). Development of novel clinically useful anticancer agents would be dependent on the screening system and the sample sources for the bioassay. Improving of simple anticancer pre-screen using convenient and inexpensive cytotoxic assay systems can offer numerous advantages as alternatives to extensive animal testing in the search for new anticancer drugs. The search for potential anticancer agents from natural sources mainly has been carried out with the guidance of bioassay confirmed by Borenfreund *et al* and the screening protocols for each tumor system have been well-established. These screening systems led to fractionate from the plants (Borenfreund *et al*. 1990). In connection with this information, we present here an exhaustive review of the literature on the cytotoxic activity, in particular, and biological activities of *Verbascum* extracts using selected bioassays and their secondary metabolites throughout the world.

New species

Verbascum eskisehirensis is confined to B3 Eskisehir in central Anatolia. A morphological comparison is made with the closely related species; *V. oreophilum* K. Koch and *V. pyramidatum* M. Bieb. (Karaveliogullari *et al*. 2009). *V. ozturkii* collected from East Anatolia in Turkey and has been described. The species is related to *V. oocarpum* Murb. and it differs from *V. oocarpum* Murb. mainly in its hair situation, basal leaves, inflorescence pedicels, calyx, corolla, stamens and capsule features (Karaveliogullari *et al*. 2008). *V. yurtkuranianum* is described and illustrated from northwest Anatolia, Turkey. It is closely related to *V. bugulifolium*, from which it differs mainly in the shape of leaves, color, corolla diameter and capsule shape (Kaynak *et al*. 2006). A new species of *Verbascum* L., *V. cicekdagensis* is described from Central Anatolia in Turkey and related to *V. wiedemannianum* Fisch. & C.A. Mey., from which it differs mainly by its leaves, bracts, and anthers (Karaveliogullari *et al*. 2006). *Verbascum tuna-ekimii* is described from E. Anatolia in Turkey. It is related to and compared with *V. laetum*, from which it mainly differs in its leaves, bracts, pedicels and capsules (Karaveliogullari *et al*. 2004). *V. azerbaijanense* is described and illustrated as a new species in northwest Iran (Azerbaijan province). It is related to *V. geminyflorum* but is distinguished from it by the length of the inflorescence, the glandular hairs of the calyx, and the absence of fertile bracteoles (Sharifnia and Assadi 2007). *V. ergin-hamzaoglui* Karavel. sp. nova (Sect. Bothrosperma Murb.) is described for the first time to the scientific community from South Anatolia in Turkey. It is related to *V. diversifolium* Hochst. and *V cymigerum* Hub.-Mor. (Karaveliogullari *et al*. 2011).

BIOLOGICAL ACTIVITIES OF *VERBASCUM* L. SPECIES

Antioxidant and cholinesterase inhibitory activity

Natural compounds are receiving increasing attention as potential antioxidants. For this purpose, in our previous studies, four flavonoid glucosides (apigenin-7-*O*-*β*-glucopyranoside, luteolin-7-*O*-*β*-glucopyranoside, luteolin-3'-*O*-*β*-glucopyranoside, and chrysoeriol-7-*O*-*β*-glucopyranoside), five phenylethanoid glycosides (verbascoside, *β*-hydroxyacteoside, forsythoside B, angoroside A, and martynoside) as well as two neolignan glycosides (dehydrodiconiferyl alcohol-9′-*O*-*β*-D-glucopyranoside and dehydrodiconiferyl alcohol-9-*O*-*β*-D-glucopyranoside) were isolated from the aerial parts of *V. salviifolium*. Additionally, harpagoside, 6-*O*-vanilloylajugol, and poliumoside were isolated from the roots of *V. lasianthum* Boiss. ex Bentham. These compounds demonstrated scavenging properties toward the DPPH radical in TLC autographic and spectrophotometric assays. They were found to have significant antioxidant properties, based on the experiments with DPPH, which indicated their ability to efficiently scavenge free radicals (Akdemir *et al*. 2004a, 2004b, 2004d).

In our other studies, free radical scavenging and cell-aggregation inhibitory activities of 36 secondary metabolites isolated from the methanolic extracts of *V. cilicicum* Boiss., *V. lasianthum* Boiss. ex Bentham, *V. pterocalycinum* var. *mutense* Hub.-Mor., *V. salviifolium* Boiss. and *V. dudleyanum* were investigated. The isolated compounds, 6-*O*-vanilloyl ajugol, ilwensisaponin A, ilwensisaponin C, verbascoside, *β*-hydroxyacteoside, martynoside, poliumoside, forsythoside B, angoroside A, dehydrodiconiferyl alcohol-9-*O*-*β*-D-glucopyranoside, dehydrodiconiferyl alcohol-9′-*O*-*β*-D-glucopyranoside, apigenin 7-*O*-*β*-glucopyranoside, luteolin 7-*O*-*β*-glucopyrano-side, luteolin 3′-*O*-*β*-glucopyranoside and chrysoeriol 7-*O*-*β*-glucopyranoside exhibited a dose-dependent inhibition of bioautographic and spectrophotometric DPPH activities. Verbascoside was the most active with IC_{50} value of 4.0 μg/ml in comparison with vitamin C (IC_{50} 4.4 μg/ml) to inhibit phorbol 12-myristate 13-acetate-induced peroxide-catalyzed oxidation of 2′, 7′-dichlorofluorescein by reactive oxygen species within human promyelocytic HL-60 cells (Tatli *et al*. 2007b, 2008c).

Our ongoing studies on biological activity of *Verbascum* species growing in Turkey, the aqueous extract of *V. mucronatum* Lam. along with its fractions and secondary metabolites were assessed for their antioxidant, AChE and BChE inhibitory activities. The antioxidant activity was evaluated by three methods: as DPPH radical scavenging activity, ferrous ion-chelating effect, and FRAP tests. The AChE activity was determined by the Ellman method using an ELISA microplate reader. The aqueous extract and fractions including verbascoside showed DPPH scavenger effect and had the best FRAP. Besides these results, one of the phenylethanoid fractions displayed the highest ferrous ion-chelating effect. While only verbascoside was found to

possess moderate AChE inhibition, the extract, fractions, and all other tested compounds (ajugol, aucubin, lasianthoside I, catalpol, ilwensisaponin A and C) did not inhibit AChE and BChE (Kahraman *et al*. 2010).

Antioxidant properties of various fractions of the methanolic extract obtained from the aerial parts of *V. macrurum* have been determined by monitoring their capacity to scavenge the stable free-radical DPPH. They were also evaluated as natural preservatives against oxidative rancidity using the accelerated Rancimat method. Ten natural compounds were identified as the components of this methanolic extract. Acteoside was the most potent free radical scavenger and showed the highest protection factor against sunflower-oil-induced oxidative rancidity (Aligiannis *et al*. 2003).

The methanolic extract of *V. wiedemannianum* Fisch. & Mey., and its phenylethanoid glycosides, wiedemannioside A-C, acteoside, martynoside, echinacoside and leukoseptoside B, were screened for possible *in vitro* antioxidant activity by two complementary test systems, namely DPPH free radical-scavenging (by bioautography and spectrophotometry) as well as β-carotene/linoleic acid test system. In the first case, *V. wiedemannianum* extract exerted an insignificant antioxidant activity. The compounds demonstrated scavenging properties toward the DPPH radical in TLC autographic assays. In the β-carotene/linoleic acid test system, *V. wiedemannianum* exhibited antioxidant activity (Abougazar *et al*. 2003; Tepe *et al*. 2006).

Pharmaceutical forms, such as capsules, tablets, a dried form as in a tea, a diluent or any delivery system prepared from the extract of *V. thapsus*, are used for the treatment of lung conditions or other degenerative conditions due to aging because of their essential antioxidant ingredients (Intelisano 2002).

The antioxidant activities of *V. xanthophoeniceum* and its secondary metabolites; forsythoside B, verbascoside and leucosceptoside B were evaluated in DPPH, oxygen radical absorbance capacity, hydroxyl radical averting capacity, FRAP, and superoxide anion ($O^{\cdot}_2^-$) radical scavenging assays. *In vitro* AChE and BChE inhibitory activities were also examined. Forsythoside B, verbascoside and leucosceptoside B proved to be effective radical scavengers and cholinesterases inhibitors (Georgiev *et al*. 2011).

The methanol and water extracts of *V. leptocladum*, *V. mucronatum* and *V. davisianum* exerted high antioxidant activity. In the DPPH free radical-scavenging and β-carotene/linoleic acid assays, the most active plant was *V. mucronatum* with 65.4 ± 0.5 µg/mL and 70.4% inhibition rate (Alan *et al*. 2009).

The methanolic extracts of *V. bottae* and *V. sinaiticum* showed free radical scavenging activity by *in vitro* DPPH assay (Motrhana *et al*. 2010; Umer *et al*. 2010).

The *in vitro* antioxidant properties of various extracts of *V. pinetorum* and *V. antiochium* were determined two complementary test systems, namely DPPH free radical scavenging and β-carotene/linoleic acid test systems. The inhibition activity of *V. pinetorum* and *V. antiochium* metanolic extracts on free radical DPPH was determined. The results provide evidence that the extracts of *V. pinetorum* contained iridoid glycosides, flavonoids, saponins and phenolic compounds which may be responsible for the substantial antioxidant activities (Ozcan *et al*. 2010, 2011).

Anti-inflammatory, antinociceptive and wound-healing activities

Inflammation is considered as a primary physiologic defense mechanism that helps body to protect itself against infection, burn, toxic chemicals, allergens or other noxious stimuli. An uncontrolled and persistent inflammation may act as an etiologic factor for many of these chronic illnesses. Although it is a defense mechanism, the complex events and mediators involved the inflammatory reaction can induce, maintain or aggravate many diseases. Currently used anti-inflammatory drugs are associated with some severe side effects. Therefore, the development of potent anti-inflammatory drugs with fewer side effects is necessary. For this purpose, in our previous studies, antinociceptive and anti-inflammatory activities of seven endemic *Verbascum* species [*V. chionophyllum* Hub.-Mor., *V. cilicicum* Boiss., *V. dudleyanum* (Hub.-Mor.) Hub.-Mor., *V. latisepalum* Hub.-Mor., *V. pycnostachyum* Boiss. & Heldr., V. *salviifolium* Boiss., *V. splendidum* Boiss.] were investigated. Antinociceptive activity was investigated via *p*-benzoquinone-induced writhing test, and the anti-inflammatory activity was studied using carrageenan-induced hind paw edema, PGE2-induced hind paw edema, and TPA-induced mouse ear edema models in mice. The methanol extracts of the flowers of *V. chionophyllum* and *V. pycnostachyum*, and the aerial parts of *V. latisepalum* and *V. salviifolium*, displayed significant antinociceptive and anti-inflammatory activity at 200 mg/kg oral dose without inducing any apparent acute toxicity or gastric damage. On the other hand, extracts from the rest of the species did not show any remarkable anti-inflammatory and antinociceptive activity (Tatli *et al*. 2008b). The methanolic extracts of 13 *Verbascum* species growing in Turkey, including *V. chionophyllum* Hub.-Mor., *V. cilicicum* Boiss., *V. dudleyanum* (Hub-Mor.) Hub.-Mor., *V. lasianthum* Boiss.. *V. latisepalum* Hub.-Mor.. *V. mucronatum* Lam., *V. olympicum* Boiss., *V. pterocalycinum* var. *mutense* Hub.-Mor., *V. pycnostachyum* Boiss. & Heldr., *V. salviifolium* Boiss., *V. splendidum* Boiss., *V. stachydifolium* Boiss. & Heldr and *V. uschackense* (Murb.) Hub.-Mor. were also assessed for their *in vivo* wound healing activity. Wound healing activities of the plants were evaluated by linear incision and circular excision experimental models subsequently histopathological analysis. The healing potential was comparatively assessed with a reference ointment Madecassol, which contains 1% extract of *Centella asiatica*. The methanolic extracts of *V. olympicum*, *V. stachydifolium* and *V. uschackense* demonstrated the highest activities on the both wound models. Moreover, the methanolic extracts of *V. latisepalum*, *V. mucronatum*, and *V. pterocalycinum* var. *mutense* were found generally highly effective. On the other hand, the rest of the species did not show any remarkable wound healing effect (Suntar *et al*. 2010).

In our other studies, *in vivo* anti-inflammatory and antinociceptive activities of *V. lasianthum* flowers and the aerial parts of *V. dudleyanum* were investigated. The methanolic extracts were shown to possess significant inhibitory activity in the carrageenan-induced hind paw edema model and in *p*-benzoquinone-induced writhings in mice. Through bioassay-guided fractionation and isolation procedures, 6-*O*-(4'''-*O*-*trans*-*p*-coumaroyl)-α-L-rhamnopyranosylaucubin, 6-*O*-(4'''-*O*-*trans*-*p*-methoxycinnamoyl)-α-L-rhamnopyranosylaucubin, sinuatol, aucubin, geniposidic acid, catalpol, ajugol and ilwensisaponin A were isolated. An iridoid glucoside, aucubin, and a triterpenoid saponin, ilwensisaponin A, were found to possess significant antinociceptive and anti-inflammatory activities, *per os* without inducing any apparent acute toxicity or gastric damage (Kupeli *et al*. 2007; Tatli *et al*. 2008c).

Saponin glycoside, ilwensisaponin C and iridoid glycosides, ajugol and picroside IV from the methanolic extract of *V. pterocalycinum* var. *mutense* were also tested for their anti-inflammatory and antinociceptive activity at doses of 100 and 200 mg/kg. Ilwensisaponin A and C showed notable activity without inducing any apparent acute toxicity as well as gastric damage. Ajugol and picroside IV had no antinociceptive and anti-inflammatory activities (Akkol *et al*. 2007).

Luteolin 7-*O*-glucoside, luteolin 3′-*O*-glucoside, apigenin 7-*O*-glucoside, chrysoeriol 7-*O*-glucoside, β-hydroxyacteoside, martynoside, forsythoside B, angoroside A, dehydrodiconiferyl alcohol-9′-*O*-β-D-glucopyranoside and dehydrodiconiferyl alcohol-9-*O*-β-D-glucopyranoside from the aqueous extract of the aerial parts of *V. salviifolium* Boiss. were studied in the *p*-benzoquinone-induced writhing reflex, for the assessment of the antinociceptive activity and

in carrageenan- and PGE1-induced hind paw edema and TPA-induced ear edema models in mice, for the assessment of the anti-inflammatory activity. Results have shown that luteolin 7-*O*-glucoside, luteolin 3′-*O*-glucoside, apigenin 7-*O*-glucoside and *β*- hydroxyacteoside significantly inhibited carrageenan-induced paw edema at a 200 mg/kg dose, while luteolin 7-*O*-glucoside, luteolin 3′-*O*-glucoside and *β*-hydroxyacteoside also displayed anti-inflammatory activity against the PGE1-induced hind paw edema model. However, all the compounds showed no effect in the TPA-induced ear edema model. The compounds luteolin 7-*O*-glucoside, luteolin 3′-*O*-glucoside also exhibited significant antinociceptive activity (Tatli *et al*. 2008a).

Moreover, the anti-inflammatory, antinociceptive and wound healing activities of *V. mucronatum* Lam. which is used as haemostatic in Turkish folk medicine (Cubukcu *et al*. 1994) were also investigated. The results of these experimental studies exhibited that *V. mucronatum* displays anti-inflammatory, antinociceptive and wound healing activities. Through bioassay-guided fractionation and isolation procedures four iridoid glucosides, ajugol, aucubin, lasianthoside I, catalpol, two saponins, ilwensisaponin A and C and a phenylethanoid glycoside, verbascoside were isolated and their structures were elucidated by spectral techniques. Verbascoside was found to possess significant wound healing activity as well as antinociceptive and anti-inflammatory potentials, per os without inducing any apparent acute toxicity or gastric damage (Akdemir *et al*. 2011).

A significant decrease in the expression and activity of iNOS and extracellular O_2- when cells were treated with verbascoside from *V. mallophorum* may have showed. Verbascoside had anti-inflammatory properties since it reduced the production of superoxide radicals and consequently reduced the activity of iNOS (Speranza *et al*. 2009).

A general correlation was suggested between the anti-inflammatory and antitumor-promoting activities of acylated saponins from Scrophulariaceae plants by Tokuda *et al*. (Tokuda *et al*. 1991). In addition to antitumor activity, songarosaponins and their acylated derivatives, which were isolated from *V. songaricum*, showed anti-inflammatory activity against the croton oil ear model.

Cytotoxic, anticancer and antitumor activities

It is well established that plants have been a useful source of clinically relevant antitumor compounds. Indeed there have been worldwide efforts to discover new anticancer agents from plants.

Common mullein (*V. thapsus* L.) is a herb with a long history of use in folk medicine and the commercial popularity of this plant has been increasing. Therefore, the potential cytotoxic activity of common mullein extracts and commercial Mullein products has been evaluated using selected bench top bioassays, antitumor and two toxicity assays (brine shrimp and radish seed). The extracts of *Verbascum thapsus* showed antitumor activity against *Agrobacterium tumefaciens*-induced tumors on potato disc method as modified by McLaughlin's group. No tumor formation was observed with camptothecin (tumor suppressant), while the tested saponins had moderate tumor inhibition. Thus, saponins are believed to be responsible for these beneficial effects. Toxicity to brine shrimp and radish seed germination and growth was observed at higher concentrations of the extracts (Turker and Camper 2002).

The effect of the fractions isolated from the aqueous extract of the flowers of *V. thapsiforme* on protein biosynthesis was studied. A strong inhibitory effect of the aqueous extract on protein biosynthesis was demonstrated in isolated rat liver ribosomes. The saponin fraction was shown to be responsible for this activity and it was compared to commercial glycyrrhizic acid and its aglycon as the reference drug. It was found that these compounds strongly inhibited the incorporation of [^{14}C] leucine into proteins *in vitro* and that the target site for inhibition was the ribosome fraction from rat liver cells (Paszkiewicz-Gadek *et al*. 1990).

Some plants have long been used in folk medicine as sources of antitumor remedies. Their effects on protein biosynthesis *in vitro* have been examined and described. The separation features of the peptide elongation system, isolated from tumoral cells, have been demonstrated. Some elongation factors or ribosomes have been shown to be a target site for the inhibition of protein biosynthesis caused by the substances isolated from various sources. Saponin glycoside and its aglycon, isolated from *V. thapsiforme* flowers, as well as digoxin, emetine, and cephaline directly inactivated ribosomes. It may be supposed that the plant inhibitors of protein biosynthesis could be utilized for searching specific antitumoral preparations (Gałasiński *et al*. 1996).

Crude extracts from plants used in traditional medicine, including *V. pseudonobile*, and extracts from plant cell cultures have been screened for potential anticancer bioactive agents, using evaluation of DNA-interaction activity. Calf thymus DNA and pUC19 (ATCC 37254) *E. coli* plasmid was evaluated in order to optimize the employed test system. The results showed that of extracts and isolated compounds, 23% proved active in DNA-interaction. Ionkova and Alferman (2000) also found that there was correlation in DNA-intercalation and the hemolytic effect in plant extracts, which contained triterpenoid saponins.

Hardman and his colleagues (Hardman *et al*. 1983) tested the seeds of uncultivated plants for lectin activity. The alcoholic extract prepared from the seeds of *V. blattaria* was tested against human red cell samples. The extract agglutinated unmodified or enzyme-modified red cells.

3, 5-dihydroxy, 6, 7-dimethoxy flavone, useful as an antiasthmatic and antiallergic, isolated from *V. thapsus*, showed 24.8% inhibition of leukotriene biosynthesis in guinea pig ileum at 1.6×10^{-5} M (Kawamo *et al*. 1988).

Investigation of the leaves of *V. sinaiticum* has afforded two flavonolignans, hydrocarpin and the novel sinaiticin, as well as two flavones, chrysoeriol and luteolin. All compounds exhibited dose-dependent cytotoxicity when tested against cultured P-388 cells (Afifi *et al*. 1993).

The compounds luteolin and 3-*O*-fucopyranosylsaikogenin F from *V. thapsus* showed promising antiproliferative activities, with an obvious effect of inducing apoptosis of A549 lung cancer cells (Zhao *et al*. 2011).

Cytotoxicity of fifty one extracts of different parts of 14 plants were studied and the activities were determined using MTT assay. The ethanol extract of *V. sinaiticum* flowers, one of the plants, showed cytotoxicity against Vero cell line (Talib and Mahasneh 2010a). *V. sinaiticum* was also evaluated *in vitro* for its antiproliferative activity against Hep-2 and MCF-7 cell lines. Plant was fractionated using ethanol, methanol, chloroform, *n*-hexane, distilled water, and butanol. The antiproliferative activity was measured by MTT assay. TLC was used to identify active fractions. The apoptotic activity of active fractions was determined using TUNEL colorimetric assay. The ethanol extract of *V. sinaiticum* exhibited high antiproliferative potential against the tested cell lines. *V. sinaiticum* flowers were more active than its aerial parts extracts (Talib and Mahasneh 2010b).

As part of our ongoing studies on the biological activities of *Verbascum* species, the *in vivo* cytotoxic activities of 13 *Verbascum* extracts including *V. chionophyllum* Hub.-Mor., *V. cilicicum* Boiss., *V. dudleyanum* (Hub.-Mor.) Hub.-Mor., *V. lasianthum* Boiss., *V. latisepalum* Hub.-Mor., *V. mucronatum* Lam., *V. olympicum* Boiss., *V. pterocalycinum* var. *mutense* Hub.-Mor., *V. pycnostachyum* Boiss. & Heldr., *V. salviifolium* Boiss., *V. splendidum* Boiss., *V. stachydifolium* Boiss. & Heldr and *V. uschackense* (Murb.) Hub.-Mor. were studied using brine shrimp (*Artemia salina*) lethality bioassay. The methanolic extracts of *V. chionophyllum* flowers and leaves, *V. cilicicum* flowers, *V. lasianthum* flowers, *V. mucronatum* flowers, *V. pycnostachyum* flowers and *V. splendidum* flowers showed the highest inhibitory activities against the brine shrimp. On the other hand, the rest of the species did not show any remarkable cytotoxic activity (Tatli *et al*. 2008). *V. chionophyllum*, *V.*

cilicicum, *V. pterocalycinum* var. *mutense*, *V. pycnostachycum* and *V. splendidum* were also studied for their cytotoxic activities against SK-MEL, KB, BT-549, and SK-OV-3 cell lines. The results were evaluated by comparing cytotoxic activity in both their methanol and ethyl acetate extracts. The methanol extract of the flowers of *V. pterocalycinum* var. *mutense* showed a weak cytotoxic activity against SK-MEL cell line. Through bioassay-guided fractionation on the methanol extract of this species, seven fractions were obtained; however, none of the fractions had cytotoxic activity against the above-mentioned cancer cell lines (Tatli and Akdemir 2006).

In order to determine the effects of 36 secondary metabolites isolated from the methanolic extracts of *V. cilicicum* Boiss., *V. lasianthum* Boiss. ex Bentham, *V. pterocalycinum* var. *mutense* Hub.-Mor., *V. salviifolium* Boiss. and *V. dudleyanum* on immunological and inflammatory reactions, they were also evaluated for their *in vitro* effects on LFA-1/ICAM-1-mediated cell aggregation using HL-60 cell line. Primary screening using cell aggregation and XTT method were reasonable assays for selection of candidates of cell adhesion inhibitors. Therefore, the isolated compounds were evaluated as having inhibitory activity for LFA-1/ICAM-1 mediated cell aggregation of HL-60 cells. Ilwensisaponin A inhibited cell aggregation (MIC 6.9 μg/ml) as compared to cytochalasin B (MIC 2.3 μg/ml). Ilwensisaponin C (MIC 62.5 μg/ml) and verbascoside (MIC 62.5 μg/ml) were weakly active in the primary cell aggregation assay, while ilwensisaponin A was >10-fold more cytotoxic (IC_{50} 4.0 μg/ml) than cytochalasin B (IC_{50} 43.0 μg/ml as determined by XTT assay). Furthermore, none of the other compounds were active in cell aggregation assay (Tatli *et al*. 2007b).

Immunomodulatory activity

Chemical constituents of four species growing in Europe, *V. phlomoides*, *V. thapsiforme*, *V. lychnitis* and *V. nigrum* were investigated and individual compounds including flavonoids, saponins and phenylpropanoids were obtained. The influence of the five isolated compounds on spontaneous proliferation of rat spleen lymphocytes was studied *in vitro*. Verbascosaponin, luteolin 7-*O*-glucoside, verbascoside and forsythoside B showed antiproliferative effect at the concentration of 100 μg/ml (87, 63, 54 and 29% suppression of [^{3}H]-thymidine uptake into DNA, respectively). At low concentration (0.1 μg/ml), verbascoside, forsythoside B and specioside revealed significant increase in proliferation (60, 64 and 53%, respectively). The results of that preliminary screening suggest immunomodulatory effects of the compounds tested (Klimek and Stepien 1994).

Antimicrobial, antimalarial and anthelmintic activity

Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. New infections can occur in hospitals resulting in high mortality. The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is stil uncertain. Therefore, actions must be taken to reduce this problem, for example, to continue studies to develop new natural drugs. The ultimate goal is to offer appropriate and efficient antimicrobial drugs to the patient. For a long period of time, plants have been a valuable source of natural products for maintaining human health, especially in the last decade, with more intensive studies for natural therapies. Some species of the genus *Verbascum* have been used by mankind for millennia to treat internal and external infections. Hildegard of Bingen, the great abbess of the early 12th century, mentions the plant in the first book of her 'Physica' under 'De Wullena', which probably referred to *Verbascum thapsus* L. (Bingen 1980).

Our ongoing pharmacological activities on *Verbascum* species, antimicrobial activities of the ethyl acetate and methanol extracts of five *Verbascum* species (the aerial parts of *V. chionophyllum* Hub.-Mor., *V. cilicicum* Boiss., *V. pterocalycinum* var. *mutense* Hub.-Mor., *V. pycnostachyum* Boiss. & Helder. and *V. splendidum* Boiss.) as well as 22 secondary metabolites isolated from the methanolic extracts of *V. cilicicum* Boiss., *V. lasianthum* Boiss. ex Bentham and *V. pterocalycinum* var. *mutense* Hub.-Mor. were studied. The materials were tested *in vitro* against *C. albicans* (ATCC 90028), *Cryptococcus neoformans* (ATCC 90113), *S. aureus* (ATCC 29213), methicillin-resistant *S. aureus* (ATCC 43300), *P. aeruginosa* (ATCC 27853), *Aspergillus fumigatus* (ATCC 90906) and *Mycobacterium intracellulare* (ATCC 23068) using a 96-well microplate assay. Amphotericin B, ciprofloxacin and rifampin were used as positive controls. Ilwensisaponin A and C showed antimicrobial activity against *A. fumigatus* ATCC 90906, but no activity was seen against Gram (+) and Gram (-) bacteria or the yeasts used in this study; none of the tested extracts or the other compounds had important antimicrobial activities. Antimalarial activities of the same extracts and compounds were also tested to *Plasmodium falciparum* clone [Sierra Leone D6 (chloroquine-sensitive)]. The antimalarial agents chloroquine and artemisinin were used as positive controls. However, none of the tested extracts or the compounds showed antimalarial activities (Akdemir *et al*. 2004c; Tatli and Akdemir 2005).

In addition, antifungal screening of 16 compounds in a matrix format from *V. lasianthum* and *V. pterocalycinum* var. *mutense*, growing in Turkey, was conducted directly on TLC plates sprayed with a spore suspension. Compounds possessing a strong antifungal activity produced a clear zone of inhibition bounded by a sharp margin regardless of the size of the inhibition zone. Ilwensisaponin A and C from *V. pterocalycinum* var. *mutense* Hub.-Mor. were found to be active. Bioautographic assay indicated that the saponins appeared to be the most effective against *Colletotrichum acutatum*, *C. fragariae* and *C. gloeosporioides* (Tatli *et al*. 2004). Ilwensisaponin A and C from the methanolic extract of the aerial parts of *V. dudleyanum* also showed potent antimicrobial activity by growth inhibition of *Aspergillus fumigatus* ATCC 90906 and both saponins were found to exhibit potent *in vitro* activity against *Colletotrichum acutatum*, *C. fragariae*, and *C. gloeosporioides* (Tatli *et al*. 2008c).

In our previous studies, methanolic extracts obtained from 13 *Verbascum* species growing in Turkey, including *V. chionophyllum* Hub.-Mor., *V. cilicicum* Boiss., *V. dudleyanum* (Hub.-Mor.) Hub.-Mor., *V. lasianthum* Boiss., *V. latisepalum* Hub.-Mor., *V. mucronatum* Lam., *V. olympicum* Boiss., *V. pterocalycinum* var. *mutense* Hub.-Mor., *V. pycnostachyum* Boiss. & Heldr., *V. salviifolium* Boiss., *V. splendidum* Boiss., *V. stachydifolium* Boiss. & Heldr. and *V. uschackense* (Murb.) Hub.-Mor. were evaluated for their *in vivo* anthelmintic activity. The extracts from *V. lasianthum*, *V. latisepalum*, *V. mucronatum* and *V. salviifolum* showed the highest inhibitory rates against *Aspiculuris tetraptera* at 100 mg/kg in mice. Additionally, extracts from *V. dudleyanum* and *V. pterocalycinum* var. *mutense* were found generally highly effective. The remaining species did not show any activity (Kozan *et al*. 2011).

The dichloromethane, ethanol:water (70:30 v/v), water and methanol extracts of *V. macrurum* leaves were tested for antimicrobial activity, and it was demonstrated that the ethanol:water extract was the most active (Guarino 2002). In a similar study, the ethanolic extract of *V. qulebrium* was subjected to phytochemical screening and it was also evaluated against six microorganisms in nutrient agar using disc agar method. This extract demonstrated the best spectrum of activity by inhibiting the growth of Gram (+) bacteria *B. subtilis* and the yeast *S. pastorianus*. The most sensitive was *S. pastorianus*, which was completely inhibited by *V. qulebrium* (10 mm) (Salim *et al*. 1996). *V. sinaiticum* also exhibited intercellular broad spectrum antimicrobial activity against Gram (+) and Gram (-) bacteria, but no activity

against the yeasts, *Candida albicans* and *C. tropicalis* (Khafagi 2001).

The extracts obtained from *V. olympicum* Boiss., *V. prusianum* Boiss., and *V. bombyciferum* Boiss. were investigated for their antimicrobial activity. It was found that *Verbascum* L. species showed antimicrobial activity against the Gram (+) bacteria and the yeast, but no activity was seen against the Gram (-) bacteria. Antimicrobial activity was most consistently detected in the species *V. prusianum* Boiss., especially against *S. aureus* ATCC 6538P, *M. luteus* La 2971, *B. megaterium* DSM 32 and *C. albicans* ATCC 10231 (Dulger *et al*. 2002).

The methanol extracts obtained from endemic *V. gypsicola* Vural & Aydogdu, *V. pseudoholotrichum* Hub.-Mor., *V. cymigerum* Hub.-Mor., *V. cholorostegium* Bornm. & Murb., *V. linguifolium* Hub.-Mor., *V. pellitum* Hub.-Mor., *V. protractum* Fenel ex Tchihat., *V. bellum* Hub.-Mor., *V. dalamanicum* Hub.-Mor. *V. chionophyllum* Hub.-Mor., *V. cilicium* Boiss., *V. trapifolium* (Stapf) Hub.-Mor., *V. meinckeanum* Murb. and *V. lyratifolium* Köchel were investigated for their antimicrobial activities by disk diffusion method. The *Verbascum* L. extracts had a strong antimicrobial activity against the Gram (+) bacteria and the yeast cultures used in this study (Dulger and Gonuz 2004; Dulger and Ugurlu 2005; Dulger *et al*. 2005; Dulger 2006).

The methanolic extracts of the leaves, flowers, roots and seeds of *V. blattaria*, *V. bombyciferum*, *V. chaixii*, *V. dumulosum*, *V. nigrum*, *V. olympicum*, *V. phlomoides*, *V. phoeniceum* and *V. roripifolium* were studied for their antimicrobial activities. The extracts had a strong antimicrobial activity against *E. coli* ATCC 11230, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 6538P and *C. albicans* ATCC 102 (Meurer-Grimes *et al*. 1996).

The flowers and leaves of *V. leptostychum* were studied for their antimicrobial activity using the single disc diffusion method. The percentage of test organisms (*E. coli*, *Proteus sp.*, *P. aeruginosa*, *Shigella dysenteriae*, *Salmonella enteritidis*, *S. typhi*, *S. aureus*, *Streptomyces faecalis*, and *C. albicans*) were susceptible to methanol plant extracts (10 and 20 µl/disc) was as follows: *V. leptostychum* flowers (11.1 and 99.9%, respectively) and leaves (22.2 and 66.6%, respectively). The water extract of *V. leptostychum* did not result in inhibition of the test organisms (Barbour *et al*. 2004).

The hydroalcoholic extract of *V. sinaiticum* was screened for its antimicrobial activity agains microorganisms, which are known to cause different types of skin infections. The tests were carried out using agar well diffusion method at three concentration levels (100, 50 and 25 mg/ml) of the crude extract. This work revealed that this species has a strong antibacterial activity against *S. aureus* and *P. aeruginosa* (Tadeg *et al*. 2005).

Turker and Camper (2002) studied the biological activity of common mullein (*V. thapsus* L.) extracts and commercial Mullein products using selected bench top bioassays, including antibacterial. The extracts were prepared in water, ethanol and methanol. Antibacterial activity (especially the water extract) was observed with *K. pneumoniae*, *S. aureus*, *Staphylococcus epidermis*, and *E. coli*.

Combined extracts of *Verbascum* flower, *Mentha piperita* and *M. crispa* leaves as well as *Cynosbata* fruits are bactericides and also agents that improve the defense of the human organism against diseases. The mixtures of the plant tissues were exhausted with ethanol and water. The extract was bactericidal *in vitro* against *S. aureus*, *Sarcina lutea*, *Shigella flexneri*, and other microorganisms (Toth *et al*. 1985).

The methanol extracts obtained from four *Verbascum* L. species (*V. cariense* Hub.-Mor., *V. adenophorum* Boiss., *V. inulifolium* Hub.-Mor. and *V. vacillans* Murb.) have been investigated for their antimicrobial activity with *Escherichia coli* ATCC 11230, *Staphylococcus aureus* ATCC 6538-P, *Klebsiella pneumoniae* UC57, *Pseudomonas aeruginosa* ATCC 27583, *Proteus vulgaris* ATCC 8427, *Bacillus cereus* ATCC 7064, *Mycobacterium smegmatis* CCM 2067, *Listeria monocytogenes* ATCC 15313, *Micrococcus luteus* CCM 169, *Candida albicans* ATCC 10231, *Rhodotorula rubra* DSM 70403, *Kluyveromyces fragilis* ATCC 8608, *Cryptococcus neoformans* ATCC 32308, *Debaryomyces hansenii* DSM 70238 and *Hanseniaspora guilliermondii* DSM 3432 by the disk diffusion method. The extracts of all plant species had strong antimicrobial activity against the Gram-positive bacteria and yeasts, but no activity was observed against the Gram-negative bacteria used in this study (Dulger and Hacioglu 2008a, 2008b).

The ethanolic extracts obtained from the leaves of *V. sinuatum* L. were investigated for their antimicrobial activities against the pathogens causing complicated urine tract infection by disk diffusion method and microdilution method. The ethanolic extracts showed strong antimicrobial activity against *Enterococcus faecalis*, *Proteus mirabilis* and *Candida albicans* Also, the extracts exhibited moderate activity against *Escherichia coli*, *Klebsiella pnemoniae*, *Pseudomonas aeruginosa* (Sener and Dulger 2009).

The methanolic extract of *V. sinuatum* showed inhibition against *Staphylococcus epidermidis* (ATCC 10875), *S. aureus* (ATCC 13709), *Enterococcus faecalis* (ATCC 14428), *Bacillus subtilis* (ATCC 10774), *Proteus vulgaris* (ATCC 12454), *Enterobacter aerogenes* (ATCC 13048), *Enterobacter cloacae* (ATCC 10699), *Klebsiella pneumoniae* (ATCC 277736), *Proteus mirabilis* (ATCC 7002), *Pseudomonas aeruginosa* (ATCC 27853), *Salmonella typhi* (ATCC 19430), *Citrobacter diversus* (ATCC 25408) with MH broth-dilution method. Generally the Gram(+) bacteria were most sensitive to the extract; among these, *S. Epidermidis* showed the lowest MIC. The Gram(−) bacteria were less sensitive; the extract showed an antibacterial activity only against *P. vulgaris*, *P. mirabilis* and *C. diversus*. Luteolin-7-glucoside, ajugol, aucubin, verbascoside, sinuatol from the methanolic extract of *V. sinuatum* inflorescences also tested for their antibacterial activities. Verbascoside showed the highest antibacterial activity, especially against *P. vulgaris* and effect all the bacteria, except *K. pneumoniae*. All compounds showed an antibacterial activity except luteolin 7-glucoside (Senatore *et al*. 2007).

Ethanol extracts of the *V. sinaiticum* flowers had potential antimicrobial activity against methicillin resistant *S. aureus*, *P. aeruginosa*, *S. typhimurium* using the microplate assay (Talib and Mahasneh 2010a).

The *in vitro* antimicrobial activity of various extracts of *V. pinetorum* was determined with agar-well diffusion method. The hexane extract exhibits antimicrobial activity against few microorganisms. The results provide evidence that the extracts of *V. pinetorum* contained iridoid glycosides, flavonoids, saponins and phenolic compounds which may be responsible for the substantial antimicrobial activity (Ozcan *et al*. 2011). The methanolic extracts of *V. bottae* also showed high antimicrobial activity against Gr (+) bacteria especially against multiresistant microorganisms by agar diffusion method (Mothana *et al*. 2010).

V. eriocarpum (flower) extract was tested on some microorganisms and found to be effective against *Staphylococcus aureus* (Benli *et al*. 2007).

Antibacterial activity of the supercritical fluid, soxlet and ultrasound-assisted extracts of the aerial parts of *V. thapsus* was performed on some strains of *Staphylococcus*, *Enterobacter cloacae* and *E. coli* isolated from clinical material of human and animal origin. Ultrasound extract showed moderately strong antibacterial effect on gram-positive bacteria for some *Staphylococcus* strains. Soxhlet extraction also showed solid antibacterial activity for *Staphylococcus* strains, but, no effect on *Enterobacter cloacae* and *E. coli.* Supercritical extract of the plant showed no antibacterial effect in the applied concentrations (Mišić *et al*. 2009).

Antibacterial activity of aqueous and alcohol extracts obtained from flowers of *V. speciosum* Schard. which were investigated considering its *in-vitro* antibacterial effect against three bacteria strains namely, *Bacillus subtilis*, *B. cereus*, and *E. coli*. The results indicated that these natural materials had an inhibitory effect on the growth. In case of

both aqueous and ethanol extracts, the maximum antibacterial activity was shown against *B. cereus* followed by *B. subtilis*, and *E. coli* was most resistant strain (Amirnia *et al*. 2011).

The extracts obtained from *V. antiochium* by increased polarity and direct methanol extraction were tested by the agar well diffusion method against various Gram-positive and Gram-negative bacteria and one fungus. The methanol/water extract exhibited a larger inhibition zone against both the Gram-negative and Gram-positive bacteria than the other extracts. *Haemophilus influenzae* was found to be the most sensitive bacterium among the bacteria tested (Ozcan *et al*. 2010).

V. songaricum have been investigated for its phytotoxic, antialgal, and antifungal activities. Two extracts of *V. songaricum* demonstrated good activity against the cyanobacterium *Oscillatoria perornata*. Through the bioactivity-guided fractionation of the water extract of *V. songaricum*, aucubin was found to be active algaecidal compound (Kobaisy *et al*. 2006).

The aqueous extract of the aerial parts of *V. fruiticulosum* demonstrated a strong growth inhibition (26.9%) towards the malaria parasite *P. falciparum* (Sathiyamoorthy *et al*. 1999).

Antiviral activity

The lyophilized infusion from the flowers of *V. thapsiforme* (FVI) Schrad. showed antiviral activity in *in vitro* studies against *Fowl plague* virus, several *Influenza A* strains, *Influenza B* strain as well as *Herpes simplex* virus. FVI has shown virucidal activity on *H. simplex* virus, but did not inactivate *Influenza* viruses (Zgorniak-Nowosielska *et al*. 1991). On the other hand, FVI reduced the infectious and haemagglutination yields of a range of *Influenza* viruses in tissue cultures. The combined application of the plant preparation FVI and three amantadine derivatives resulted in a marked enhancement of the inhibitory effect of FVI on the reproduction of *Influenza* virus A/chicken/Germany/27, strain Weybridge (H7N7) in cell cultures of chicken embryo fibroblasts. The most pronounced enhancement was shown for the combination of FVI and adamantanamine glucuronide (Serkedjieva 2000).

Antiviral activity of the alcoholic extract of *V. thapsus* has been studied. The tests were carried out in Vero cells-*Pseudorabies* virus strain RC/79 (*Herpes suis* virus) system. Maximum non-cytotoxic concentration was 1.40 mg plant material *per* ml. The leaf extract of *V. thapsus* was able to inhibit the viral infectivity (Zanon *et al*. 1999). *V. thapsus* has also been investigated for *in vitro* antiviral activity against Herpes simplex virus type 1 (HSV-1) and influenza virus A by dye uptake assay in the systems HSV-1/Vero cells and influenza virus A/MDCK cells. The methanolic extract of *V. thapsus* exerted strong anti-influenza viral activity (Rajbhandari *et al*. 2009).

In another study, one hundred methanolic plant extracts were screened for their antiviral activity against seven viruses. Twelve extracts were found to have antiviral activity at the non-cytotoxic concentrations tested. The extracts prepared from *V. thapsus* exhibited antiviral activity against *Herpes* virus type 1 (McCutcheon *et al*. 1995).

Antitussive activity

Antitussive activity of *V. thapsiforme* carbohydrate substances was tested on conscious cats by mechanical stimulation of the laryngopharyngeal and tracheobronchial mucous areas of the airways through a surgically implanted endotracheal cannula. Parameters of the cough reflex were registered and statistically evaluated. Comparative tests with commonly used antitussive drugs from both narcotic (codeine) and non-narcotic (dropropizine) groups were also carried out under the same conditions. Comparison of the cough suppressive ability of the classical drugs revealed that the antitussive effect of these carbohydrates was lower than of codeine but significantly higher than that of dropropizine. Expectoration parameters were reduced minimally after orally administrated herbal agents (Nosalova *et al*. 2005).

Anti-ulcerogenic activity

Several plants containing high amounts of saponins have been shown to possess anti-ulcerogenic activity in several experimental ulcer models. The protective activities of these saponins may be due to the activation of mucous membrane protective factors and inhibition of gastric secretion volume and acid secretion. Many phytochemical analyses led to the isolation of mucilages, flavonoids, phenylethanoids and saponins from the inflorescence of some *Verbascum* species. Consequently, data on the phytochemistry of *Verbascum* sp. suggested that investigation of the anti-ulcerogenic activity of the flowers of *V. cheiranthifolium* Boiss. var. *cheiranthifolium* could be a promising approach. The water extract of *V. cheiranthifolium* Boiss. var. *cheiranthifolium* given orally was tested for gastric protection against ethanol-induced gastric ulcer model in rats. However, no rat was completely protected from any visible damage (Gurbuz *et al*. 2005).

Hepatoprotective effect

V. sinaiticum was searched for its hepatoprotective activity against CCl_4-induced hepatotoxicity in Swiss albino mice by evaluating the levels of hepatic marker enzymes, ALT, AST and ALP. The results revealed that pretreating mice with the hydro-alcoholic extracts of *V. sinaiticum* significantly suppressed the plasma AST and ALT activity when compared with the CCl_4 intoxicated control (Mahmoud *et al*. 2007; Umer *et al*. 2010).

V. thapsus L. was evaluated for its antihepatoma activity on five human liver-cancer cell lines. The crude drug demonstrated *in vitro* growth inhibition against HepG2/C3 and HA22T/VGH (Lin *et al*. 2002).

A biostimulating herbal mixture for use in hematopoietic, liver and respiratory disorders in humans comprises propolis extract (15% flavonoids as chrysin) 0.075, *Gratiola* extract, *Verbascum* extract 0.075, *G. officinalis* powder 0.005, and pollen 0.04 parts. Thus, a tablet formulation contained *per* tablet propolis 0.15, *G. officinalis* 0.005, pollen 0.040, starch 0.013, aerosol 0.010, talc 0.005, and lactose 0.55 g (Paunescu 1985).

Antihyperlipidemic activity

In rats with induced hyperlipidemia, polysaccharides obtained from the leaves of *V. thapsus* exhibited a significant decrease in cholesterol and triglyceride levels (Aboutabl *et al*. 1999).

Pesticidal activity

The ethanolic extract from the flowers of *V. cheiranthifolium* was examined for its effect on mortality and progeny production against adults of *Rhyzopertha dominica* on two commodities, wheat and barley. Results indicated that mortality was 100% on wheat and 63% on barley after the test (Khoshnoud *et al*. 2008b). The ethanolic extract was also examined for its effect on mortality and progeny production against adults of *Sitophilus oryzae* and *Tribolium castaneum*. *S. oryzae* was more sensitive than *T. castaneum* and complete suppression of the progeny production was observed in the treated wheat than in the untreated wheat even in the lowest dose rate for two species (Khoshnoud and Khayamy 2008). Additionally, *V. speciosum* were researched for their effect on mortality and progeny production against adults of *Sitophilus oryzae*. However, *V. cheiranthifolium* extract was more effective than *V. speciosum* against adult insects. In two cases complete suppression (100% reduction) of the progeny production was observed in the treated wheat than in control even in the lowest dose rate (Khoshnoud *et al*.

2008a).

Phytogrowth-inhibitory activity (antigermination activity)

The methanolic extract of *V. sinuatum* inflorescences and the isolated secondary metabolites luteolin-7-glucoside, ajugol, aucubin, verbascoside, sinuatol from the extract studied for their allelopathic activity on radish. Allelopathic activity using a bioassay based on seed germination and subsequent radicle growth. Ajugol showed an activity similar to crude extract. Aucubin and sinuatol showed inhibiting activity while verbascoside showed the highest inhibiting activity (Senatore *et al*. 2007).

The methanolic extracts of *V. speciosum* were tested for genotoxic and inhibitor activity against *Zea mays* seed. The methanol extracts of leaf, stem, and root of *V. speciosum* applied to *Zea mays* seed. The results showed that especially 10% diluted leaf, stem and root extracts had a strong inhibitory activity. Also, different concentration methanolic extract caused a decrease mitotic index and an increase chromosomal aberration, and changed RAPD profiles (Sunar *et al*. 2009).

Pardo *et al*. (1998, 2004) investigated phytotoxins from an ethanolic extract of the dried aerial parts of *V. virgatum* and the roots of *V. thapsus*, which exhibited antigermination activity on the seeds of barley (*Hordeum vulgare*). The extracts led to isolation of iridoid glycosides, which are known to inhibit plant growth.

Other activities

Cuñat *et al*. (Cuñat *et al*. 1990) screened plant species of the Spanish Mediterranean flora for juvenile hormone-mimic by alteration of *Tribolium castaneum* metamorphosis. *V. sinuatum* had important juvenile hormone activity, inducing severe metamorphical disturbances affecting over 75% of the treated insects.

The extract prepared from *V. thapsus* demonstrated its ability to inhibit one or more extracellular proteases, which degrade human tissue matrix (Cyr 2002).

Krushkov and his colleagues (Krushkov *et al*. 1970) established that an alkaloid (nobilin) obtained from *V. nobile* Vel. has ganglion-blocking and myotropic vasodilative effects, which explains their hypotensive action.

Otitis media is one of the most frequent diseases of early infancy and childhood and one of the most common reasons for children to visit a physician. Therefore, children were randomly assigned to receive treatment with NHED, including *V. thapsus*, with or without amoxicillin. This study suggests that in cases of ear pain caused by acute otitis media in children in whom active treatment, besides a simple 2- to 3-day waiting period, is needed, an herbal extract solution may be beneficial (Sarrell *et al*. 2003).

Psoriasis is a skin disease that manifests itself as blotches, a silver-colored peeling and a hardening of the skin (paraketosis). In the framework of traditional medicine, the use of some plants (including *V. sinuatum* L.) typical of the flora of Sicily in the treatment of psoriasis has been reported. The aerial parts of the plants are collected in spring and used to make a decoction, which is prepared in 10% alcohol. Significant improvement in the pathology may be noted and in some cases complete recovery is observed (Amenta *et al*. 2000).

Cosmetics, bath preparations, and detergents contain extracts of plants selected from *Trifolium pretense*, *Gerbera jamesonii*, *Tulipa gesneriana*, *Helianthus annuus*, *Dianthus caryophyllus*, *Trifolium repens*, *Rosa*, *Magnolia lilifolia*, *V. thapsus* and *V. thapsiforme*. A milky lotion containing these plant extracts showed skin moisturizing and conditioning effects (Ohara *et al*. 2001).

A composition for use as a tobacco substitute and as an aid in the cessation of tobacco use contains *V. thapsus*, an algae, *Medicago sativa*, and *Symphytum officinale*, together with other optional components. Use of the present invention as a tobacco substitute in cigarettes or pipes produces a diminished desire for tobacco (Coy-Herbert 2002).

The heavy metal content and accumulation capabilities of *V. bombyciferum* were tested and the results showed that this plant can be used as a bio-indicator species in the monitoring of increased Cd^{2+}, Cr^{3+}, Pb^{2+}, and Zn^{2+} in the environment (Arslan *et al*. 2010). Moreover, metal intake abilities of *V. cheiranthifolium* were studied and for this aim, metal contents (Mo, Cu, Pb, Zn, Ag, As and Cd) of dried plants and soil were determined and correlated. The plant took up metals in high amounts - as high as hundreds of times more than averages for non-hyperaccumulator plants (Sagiroglu *et al*. 2006). The distribution and accumulation of strontium (Sr) in the shoots and roots of *V. cheiranthifolium* was also investigated. It's found that plant can be an efficient bioaccumulator for Sr and it can be used in cleaning or rehabilitating of the contaminated soil and areas by Sr (Sasmaz and Sasmaz 2009). Besides these, heavy metal content (Cu, Fe, Mn, Ni, Pb, Zn) was determined in soils and different organs of *V. olympicum* using an atomic absorption spectrophotometer. The results of the experiment suggested that this species may be useful as a bioindicator for heavy metals (Guleryuz *et al*. 2006).

The methanolic extract of *V. sinaiticum* was searched for schistosomicidal activity and could represent promising bioactive sources that deserve further investigation (Yousif *et al*. 2007).

CHEMICAL CONSTITUENTS

Tatli and Akdemir (2004) were reviewed the chemical constituents of *Verbascum* species dated from the year 2004 (Tatli and Akdemir 2004). In the present study, the compounds in *Verbascum* species are classified as six main groups, such as saponins, iridoid glycosides, phenylethanoid glycosides, neolignan glucosides, flavonoids and asetophenone glucoside. The major skeleton of each main group is given in the relevant section. The structures are represented in the tables from the basic to the complex skeleton, together with distribution in plants in alphabetical order (*recorded species in the Flora of Turkey and our group studied on these species).

Saponins

This is one of the major group in the genus *Verbascum*. The phytochemical studies on these species have revealed the presence of oleanane type triterpene saponins, usually monodesmosidic and their sugar moiety are attached at C-3 (OH) (**Fig. 1**). The saponins in *Verbascum* species were given in **Table 1**.

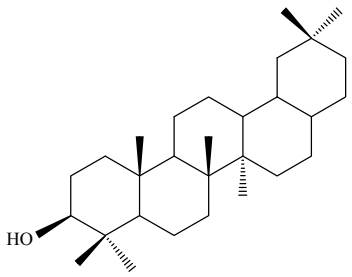

Fig. 1 Chemical structure of saponins in *Verbascum* species.

Table 1 Saponins of *Verbascum* L. species.

Saponins	Species	References
Ilwensisaponin A	*V. dudleyanum**	Tatli *et al*. 2008c
	*V. lasianthum**	Tatli *et al*. 2006
	*V. mucronatum**	Akdemir *et al*. 2011
	V. thapsus	Turker *et al*. 2004
Ilwensisaponin C	*V. dudleyanum**	Tatli *et al*. 2008c
	*V. mucronatum**	Akdemir *et al*. 2011
Verbascosaponin	*V. ballii*	Arrif *et al*. 2006

Table 2 Iridoid glycosides of *Verbascum* L. species.

Iridoid glycosides	Species	References
Aucubin	*V. conocarpum*	Ramunno *et al*. 2006
	V. densiflorum	Gvazava and Kikoladze 2009
	V. dentifolium	Arrif *et al*. 2008
	*V. dudleyanum**	Tatli *et al*. 2008c
	*V. lasianthum**	Tatli *et al*. 2006
	*V. mucronatum**	Akdemir *et al*. 2011
	V. phlomoides	Gvazava and Kikoladze 2009
	*V. pycnostachyum**	Tatli *et al*. 2007a
	V. sinaiticum	Mahmoud *et al*. 2007
Geniposidic acid	*V. lasianthum**	Tatli *et al*. 2006
6-*O*-*β*-D-glucopyranosylaucubin	*V. salviifolium**	Akdemir *et al*. 2005
Sinuatol	*V. lasianthum**	Tatli *et al*. 2006
6-*O*-*β*-D-xylopyranosylaucubin	*V. phlomoides*	Gvazava and Kikoladze 2009
6-*O*-(4″-*O*-*trans*-*p*-coumaroyl)-*α*-L-rhamnopyranosylaucubin	*V. lasianthum**	Tatli *et al*. 2006
6-*O*-(4″-*O*-*trans*-*p*-methoxycinnamoyl)-*α*-L-rhamnopyranosylaucubin	*V. lasianthum**	Tatli *et al*. 2006
6-*O*-(6″-*O*-*trans*-*p*-hydroxycinnamoyl)-*β*-D-glucopyranosylaucubin	*V. salviifolium**	Akdemir *et al*. 2005
Odontoside	*V. oreophilum*	Danchul *et al*. 2006
Catalpol	*V. conocarpum*	Ramunno *et al*. 2006
	V. densiflorum	Gvazava and Kikoladze 2009
	*V. dudleyanum**	Tatli *et al*. 2008c
	*V. lasianthum**	Tatli *et al*. 2006
	*V. mucronatum**	Akdemir *et al*. 2011
	V. phlomoides	Gvazava and Kikoladze 2009
6-*O*-*β*-D-glucopyranosylcatalpol	*V. salviifolium**	Akdemir *et al*. 2005
6-*O*-*α*-L-rhamnopyranosylcatalpol	*V. salviifolium**	Akdemir *et al*. 2005
	*V. dudleyanum**	Tatli *et al*. 2008c
Saccatoside	*V. nigrum*	Danchul *et al*. 2006
	V. phlomoides	Gvazava and Kikoladze 2009
6-*O*-(2″-*O*-*trans*-cinnamoyl)-*α*-L-rhamnopyranosylcatalpol (=verbaspinoside)	*V. salviifolium**	Akdemir *et al*. 2005
6-*O*-(3″-*O*-*trans*-*p*-coumaroyl)-*α*-L-rhamnopyranosylcatalpol	*V. dudleyanum**	Tatli *et al*. 2008c
6-*O*-[(2″-*O*-*p*-methoxy-*cis*-cinnamoyl-3″-*O*-acetyl)-*α*-L-rhamnopyranosyl]-catalpol	*V. dentifolium*	Arrif *et al*. 2008
6-*O*-[(2″-*O*-*p*-methoxy-*trans*-cinnamoyl-3″-*O*-acetyl)-*α*-L-rhamnopyranosyl]-catalpol	*V. dentifolium*	Arrif *et al*. 2008
(=Pulverulentoside I)	*V. salviifolium**	Akdemir *et al*. 2005
6-*O*-(4″-*p*-methoxy-*trans*-cinnamoyl)-*α*-L-rhamnopyranosylcatalpol	*V. densiflorum*	Gvazava and Kikoladze 2009
Verbascoside A	*V. alpigenum*	Danchul *et al*. 2006
	V. blattaria	Danchul *et al*. 2006
	V. densiflorum (=*V. thapsiforme*)	Danchul *et al*. 2006
	V. flavidum	Danchul *et al*. 2006
	V. formosum	Danchul *et al*. 2006
	V. hajastanicum	Danchul *et al*. 2006
	V. laxum	Danchul *et al*. 2006
	V. macrocarpum	Danchul *et al*. 2006
	V. oreophilum (=*V. aureum*)	Danchul *et al*. 2006
	V. pyramidatum	Danchul *et al*. 2006
	V. wilhelmsianum	Danchul *et al*. 2006
Picroside IV	*V. thapsus*	Hussain *et al*. 2009
Angeloside	*V. dentifolium*	Arrif *et al*. 2008
Vaniloylangeloside	*V. dentifolium*	Arrif *et al*. 2008
6-*O*-(4″-*O*-*trans*-3,4-dimethoxycinnamoyl)-*α*-L-rhamnopyranosylcatalpol	*V. salviifolium**	Akdemir *et al*. 2005
(=Buddlejoside A_8)		
Scrospioside A	*V. ballii*	Arrif *et al*. 2006
Scropolioside B	*V. ballii*	Arrif *et al*. 2006
Ajugol	*V. dudleyanum**	Tatli *et al*. 2008c
	*V. lasianthum**	Tatli *et al*. 2006
	*V. mucronatum**	Akdemir *et al*. 2011
	*V. pycnostachyum**	Tatli *et al*. 2007a
	V. sinaiticum	Mahmoud *et al*. 2007
	V. thapsus	Hussain *et al*. 2009
Harpagide	*V. densiflorum*	Gvazava and Kikoladze 2009
	V. dentifolium	Arrif *et al*. 2008
Harpagide acetate	*V. densiflorum*	Gvazava and Kikoladze 2009
Ajugoside	*V. pycnostachyum**	Tatli *et al*. 2007a
Laterioside	*V. thapsus*	Hussain *et al*. 2009
Harpagoside	*V. dentifolium*	Arrif *et al*. 2008
	*V. pycnostachyum**	Tatli *et al*. 2007a
	V. thapsus	Hussain *et al*. 2009
Lasianthoside I	*V. mucronatum**	Akdemir *et al*. 2011
Verbathasin A	*V. thapsus*	Zhao *et al*. 2011

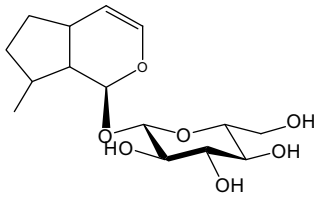

Fig. 2 Chemical structure of iridoids in *Verbascum* species.

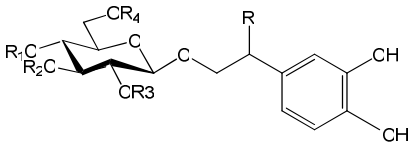

Fig. 3 Chemical structure of phenylethanoids in *Verbascum* species.

Table 3 Phenylethanoid glycosides of *Verbascum* L. species.

Phenylethanoid glycosides	Species	References
Verbascoside	*V. conocarpum*	Ramunno *et al*. 2006
(=Acteoside)	*V. densiflorum*	Klimek *et al*. 2010
	*V. mucronatum**	Akdemir *et al*. 2011
	V. phlomoides	Gvazava and Kikoladze 2007; Klimek *et al*. 2010
	*V. pycnostachyum**	Tatli *et al*. 2007a
	*V. salviifolium**	Akdemir *et al*. 2004d
	V. thapsus	Hussain *et al*. 2009
	V. xanthophoeniceum	Georgiev *et al*. 2011
β-hydroxyacteoside	*V. salviifolium**	Akdemir *et al*. 2004d
Martynoside	*V. salviifolium**	Akdemir *et al*. 2004d
Forsythoside B	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
	*V. salviifolium**	Akdemir *et al*. 2004d
	V. xanthophoeniceum	Georgiev *et al*. 2011
Angoroside A	*V. salviifolium**	Akdemir *et al*. 2004d
Leucosceptoside	*V. xanthophoeniceum*	Georgiev *et al*. 2011

Iridoid glycosides

Iridoids, represent a large group of cyclopentano[*c*]pyran monoterpenoids, are found as natural constituents in a large number of *Verbascum* species. A bicyclic H-5/H-9 *β*,*β*-*cis*-fused cyclopentanopyran ring system is the most common structural features of these substances. They also contain a double bond between C-3 and C-4 including non-substitution at C-4 (**Fig. 2**). *Verbascum* species contain especially aucubin and catalpol type iridoids and their acylated derivatives were modificated with aliphatic and aromatic acids (e.g. acetic acid, *trans*-cinnamic acid, *trans*-*p*-coumaric acid, ferulic acid) and these glycosides were also variated with the esterification positions. The iridoid glycosides in *Verbascum* species were shown in **Table 2**.

Phenylethanoid glycosides

Phenylethanoid glycosides are natural polyphenolic compounds widely in many Dicotyledone families, and also rich in *Verbascum* genus. Structurally, they are characterized as glycosides of phenylethanol, esterified at R_1 position by a cinnamic, caffeic and ferulic acid derivatives. Attachment of the increasing number of sugar units (up to now, mono, di, tri), the types of the sugars (glucose, rhamnose, arabinose, apiose and xylose), different sequence (R_2-R_4) and substitutions cause a great variations in their structures (**Fig. 3**). The phenylethanoid glycosides in *Verbascum* species were given in **Table 3**.

Neolignan glucosides

Lignans and neolignans belong to an important group of natural products, consisting of two phenylpropane monomers linked through carbon-carbon or carbon-oxygen bonds.

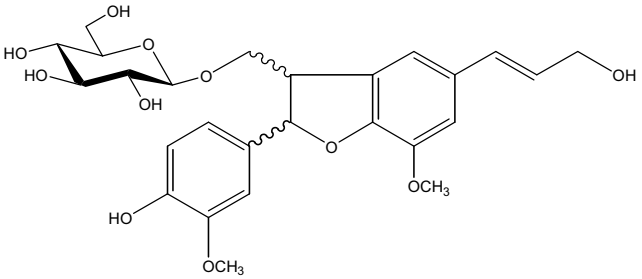

Fig. 4 Chemical structure of neolignans in *Verbascum* species.

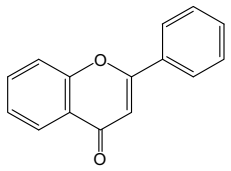

Fig. 5 Chemical structure of flavonoids in *Verbascum* species.

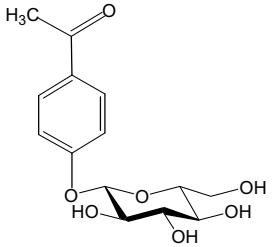

Fig. 6 Acetophenone glucoside in *Verbascum* species.

The neolignan glucosides, from *Verbascum* species have dehydrodiconiferyl alcohol skeleton (**Fig. 4**). The neolignan glycosides in *Verbascum* species were given in **Table 4**.

Flavonoids

The flavonoid glycosides are widely distributed in the plant kingdom. They have benzo-γ-pyrone skeleton in their structure (**Fig. 5**). Until now, many flavonoids were reported from *Verbascum* species in which there was a large variety of flavone and flavonol aglycones such as apigenin, luteolin, quercetin and kaempherol. Glycosylation was usually at C-7 position of these aglycones. On the other hand, a C-glucoside was found in *V. cherianthifolium*. Isoflavone and flavonolignans from *V. sinaiticum* were also observed. The flavonoids from *Verbascum* species were seen in **Table 5**.

Acetophenone glucoside

The acetophenone glucoside (**Fig. 6**) from *Verbascum* species was seen in **Table 6**.

Other compounds

Buddlindeterpene A, B, C, (+)-genipin, *α*-gardiol, *β*-gardiol were isolated from the methanolic extract of *V. thapsus* (Hussain *et al*. 2009).

Pentadecane (58.2%), tetradecane (9.0%), tricosane (6.4%), pentacosane (6.0%) and benzene acetaldehyde (3.9%) were determined in the flower oil; (*2E*)-hexenal (33.2%), palmitic acid (7.1%), (*2E*,*4Z*)-heptadienal (6.6%), pentacosane (6.2%), allo-ocimene (5.8%) in the leaf oil; palmitic acid (24.6%), tetracosane (18.3%), pentacosane (5.9%), pentadecenal (5.9%) and (*2E*)-hexenal (5.2%) in the stem oil of *V. wiedemannianum* as major components by GC and GC-MS (Iskender *et al*. 2009). Major components, 1-octen-3-ol (22.5%), *α*-bisabolol (10.6%) and nonanal (9.0%) were determined in the essential oil of the aerial parts of *V. undulatum* Lam. by GC and GC/MS, as well (Melliou *et al*. 2007).

Table 4 Neolignan glucosides of *Verbascum* L. species.

Neolignan glucosides	Species	References
Dehydrodiconiferyl alcohol-9′-*O*-*β*-D-glucopyranoside	*V. salviifolium**	Akdemir *et al*. 2004d
Dehydrodiconiferyl alcohol-9-*O*-*β*-D-glucopyranoside	*V. salviifolium**	Akdemir *et al*. 2004d

Table 5 Flavonoids of *Verbascum* L. species.

Flavonoids	Species	References
Apigenin	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
Apigenin-7-*O*-*β*-glucopyranoside	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
Luteolin	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
	V. sinaiticum	Mahmoud *et al*. 2007
Luteolin-7-*O*-*β*-glucopyranoside	*V. densiflorum*	Klimek *et al*. 2010
	*V. dudleyanum**	Tatli *et al*. 2008c
	V. phlomoides	Klimek *et al*. 2010
	V. sinuatum	Senatore *et al*. 2007
Diosmin	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
Chrysoeriol-7-glucoside	*V. sinaiticum*	Mahmoud *et al*. 2007
Quercetin-7-*O*-*β*-glucopyranoside	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
Tamarixetin-7-glucoside	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
Tamarixetin-7-rutinoside	*V. densiflorum*	Klimek *et al*. 2010
	V. phlomoides	Klimek *et al*. 2010
Amentoflavone	*V. thapsus*	Hussain *et al*. 2009

Table 6 Acetophenone glucoside of *Verbascum* L. species.

Acetophenone glucoside	Species	References
Picein	*V. dudleyanum**	Tatli *et al*. 2008c

CONCLUSION

A wide range of biological activities have been determined from *Verbascum* extracts, including antioxidant, anti-inflammatory, cytotoxic, antitumor, immunomodulatory and antimicrobial activities, which have been reviewed from our studies and the related literatures. Some of these effects may be attributed to the use of these species in folk medicine.

The isolated compounds from *Verbascum* species were evaluated under six main groups. It was considered that iridoid glycosides, flavonoids, phenylethanoid glycosides and saponins, respectively, are obtained in the plants more than the others and they may be responsible for the biological activities which are mentioned above. In consideration of the claimed biological activities of *Verbascum* species, it is not necessarily a single compound that is responsible for these effects; they may be due to several compounds acting in a synergistic manner or to the regulation of one compound by another.

Due to the very long tradition of using *Verbascum* species in several types of diseases, it seems worthwhile to explore these species further. In our ongoing project, developing on officinal preparations from some endemic *Verbascum* species growing in Turkey will be useful.

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