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Review Article

Common mullein, pharmacological and chemical aspects

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A B S T R A C T

Verbascum thapsus L. [Khardhag or Common mullein], a member of the family Scrophulariaceae, is a famous herb that is found all over Europe, in temperate Asia, in North America and is well-reputed due to its medicinal properties. This medicinal herb contains various chemical constituents like saponins, iridoid and phenylethanoid glycosides, flavonoids, vitamin C and minerals. It is famous in various communities worldwide for the treatment of various disorders of both humans and animals ailments. A number of pharmacological activities such as anti-inflammatory, antioxidant, anticancer, antimicrobial, antiviral, antihepatotoxic and anti-hyperlipidemic activity have been ascribed to this plant. The plant is used to treat tuberculosis also, earache and bronchitis. In the present paper botanical and ethnomedicinal description, pharmacological profile and phytochemistry of this herb is being discussed.

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Introduction

The origin of majority of remedies, recipes and pharmaceuticals has been traced to medicinal plants. There is increasing trend of investigating the pharmacological potential of the extracts, fractions and compounds isolated from plant species, the *in vivo* investigations of toxicity and biological activities of extracts or bioactives, the possible mechanisms of action involved, and the standardization and chemical characterization of the extracts. *Verbascum* is the largest genus of the family Scrophulariaceae, with about 2500 species (Tatli and Akdemir, 2006). *Verbascum thapsus* L. is an important species of this genus and is found wild on stony ground, in wasteland, woodland, clearings and roadsides (Speranza et al., 2010). The use of *Verbascum thapsus* increasing the medicines not only globally but in developing countries

also in advanced countries (Turker and Camper, 2002) where the United States like dried leaves and flowers, capsules, alcoholic extracts and the flower oil of this plant can easily be found in health stores (Turker and Gurel, 2005). The present work is a critical survey of research carried out on this important medicinal plant. Electronic search engines like Scifinder® and Science Direct were used to search the isolated bioactive constituents and pharmacological activities exhibited by these compounds as well as by the crude extracts by using the search-terms common mullein, *Verbascum thapsus*, chemical constituents and pharmacological activities as keywords. The information in the present work will serve as baseline data and may inspire new biomedical applications of *V. thapsus*, especially isolation of bioactive products and their practical use as patents.

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Botanical aspects

Etymology of name

The *Verbascum* is derived from Latin word meaning *barbascum* barba or beard (Jankowiak, 1976) referring to the plant's beardlike filaments (Wilhelm, 1974). There are various myths regarding the term *Thapsus* as it may have been derived from the Isle of Sicilian Thapsos where mullein was gathered in ancient times (Muenscher, 1935) or from the Tunisian Island "Thapsos" (Jankowiak, 1976). "Thapsos" is Greek word representing the yellow flower of the plant (Wilhelm, 1974). The plant has yellow flowers are Roman ladies their hair dyed yellow (DeBray, 1978). Mullein the word is derived from the Latin *mollis*, or soft (Durant, 1976), which is synonymous to the present term woolen (Muenscher, 1935; Mitich, 1983).

Common names

Adam's flannel, Aaron's rod, Beggar's blanket, Beggar's stalk, Big taper, Blanket herb, Bullock's lungwort, Candlewick plant, Clot, Clown's lungwort, Common mullein, Cuddy's lungs, Duffle, Feltwort, Flannel mullein, Flannel plant, Flannel leaf, Fluffweed, Golden rod, Hare's beard, Hag's taper, Jacob's staff, Jupiter's staff, White mullein, Mullein dock, Old man's flannel, Our lady's flannel, Peter's staff, Rag paper, Shepherd's staff, Shepherd's clubs, Torches, Velvet dock, Velvet plant, Woollen and Wild ice leaf. So many names indicate friendly, majestic, plain old and soft image of the plant in minds (Britton and Brown, 1898; Durant, 1976; Brickell and Zuk, 1997; Wagner et al., 1999).

Local names in Pakistan

Locally *Verbascum thapsus* L. is named as Kharghwug (Murad et al., 2011), Ghordoughkaro (Hussain et al., 2007), Gidder Tambakoo (Qureshi et al., 2007), Tamakusak (Shinwari and Gilani, 2003), Khardhag (Sher, 2011), Jungle tambako and barbasco (Pullaiah, 2003).

Habitat and distribution

Verbascum thapsus L. grows wild on stony ground, in wasteland, woodland, clearings and roadsides (Turker and Gurel, 2005). It is distributed in different areas of Pakistani like Kurram Agency, Dir, Chitral, Swat, Gilgit, Deosai, Baltistan, Drass, Ladakh, Hazara, Kashmir, Baluchistan and Punjab (Shinwari and Gilani, 2003). It is widely distributed plant, being found all over Europe, temperate and temperate Asia in the Himalayas to the far, abundant in North America as a naturalized weed in the eastern States (Murbeck, 1933; Hoshovsky, 1986; Ansari and Daehler, 2000).

Plant description

V. thapsus is an herbaceous annual or biennial, erect and stout weed. It produces a low vegetative rosette up to 61 cm. Flowers are densely arranged, occur usually one per axil five having

both male and female reproductive organs. Flowers are yellow in color having five sepals, five petals, two-celled ovary and five stamens. Fruit is in the form of capsule that split into two valves at maturity. Capsule has star shaped appearance and ovoid having 3-6 mm length. The fruit contain seeds that are brown in color having 0.5-1.0 mm length. Basal leaves are oblong-obovate to oblanceolate entire generally, having short and long petioles (10-40 cm).

Leaves margins are entire or obscurely crenate and alternately arranged. Leaves arranged along the stem (cauline leaves) are 5-30 cm in length having pinnate venation. Mullein has a deep taproot with a fibrous root system shallow secondary. Stem is erect and stout having 50 to 180 cm range of tallness. The stem is simple generally having alternately arranged leaves (Wagner et al., 1999; Halvorson and Guertin, 2003; Remaley, 2005). The plant produces up to 100,000-180,000 numerous seeds per plant during the second or third year of growth, and can remain dormant for greater than 100 years (Gross and Werner, 1982). The capsule contain seeds that are brown in color having length 0.5-1.0 mm, oblong-prismatic seed shape and seed surface ornamented by irregular polygonal cells with or without distinct vesicles (Attar et al., 2007; Kinsman, 2008; Mahek et al., 2011).

Traditional uses

Common mullein has an old relationship with man and is respected because of mystical and medicinal powers traditionally. According to old herbalists if someone keeps a part of the plant it has the ability to keep away evil spirits and terrors (Muenscher, 1935; DeBray, 1978). It was famous among Greeks that Ulysses took this plant to protect him against the wiles of Circe (DeBray, 1978). Greeks, Romans and people of Western United States knew it as candle/torch are they used it at funerals or other holy ceremonies (Muenscher, 1935). The people of Rome and Ireland called it "lungwort" because of its use to cure lung disease in both humans and livestock (Muenscher, 1935; DeBray, 1978). Few folk's names of the plant shows its association with Christianity and medieval beliefs in witches; those are Lady's candle, Lady's flannel, Our Lady's taper, Lady's candle stick, Virgin Mary's candle, Woolly mullein and Hag's Taper (McLeod, 2008).

The flowers and leaves are analgesic, anti-inflammatory, antiseptic, spasmolytic, astringent, diuretic, emollient, expectorant and vulnerary (DeBray, 1978; Grieve, 1981; Chiej, 1984; Hussain et al., 2007). Homeopathic formulations containing fresh leaves are used in the treatment of long-standing headaches accompanied with oppression of the ear (Grieve, 1981). Ointments prepared from leaves are used for burns and earache (Haughton, 1978). Topically, the poultice of the leaves is a good healer of wounds and is also applied to ulcers, tumors and piles. A poultice made from the seeds and leaves is used to draw out splinters (Grieve, 1981).

Infusion of the flowers in olive oil is used as earache drops having strong bactericidal properties (Bown, 1995; Chevallier, 1996). An infusion or tea of the plant is taken internally in the treatment of a wide range of chest and abdominal complaints including productive cough and diarrhea (Bown, 1995; Chevallier, 1996; Murad et al., 2011). It is used as a tobacco substitute (Wilhelm, 1974) and rheumatic problems (Haughton, 1978).

A decoction of the seeds is used to soothe chilblains and chapped skin (Chiej, 1984). The juice of the plant and powder made from the dried roots is said to quickly remove rough warts when rubbed on them. A decoction of the roots is said to soothe and relieve also cramps and convulsions alleviate (Grieve, 1981).

General uses

Flower extract in hot water is used as dye to turn hair a golden color (Grieve, 1981; Huxley, 1992) that can be changed to green dye on acidification or alkalization on to brown. Leaves are used in the insulation shoes to keep the feet warm (Grieve, 1981). Also mullein was used as a useful fish poison (Haughton, 1978). The stems are used as torches, tinder and wicks for candles (DeBray, 1978; Grieve, 1981; RHS, 1988).

Physico-chemical parameters

Physicochemical parameters provide an idea about the drug purity, inorganic composition and the total solvent soluble component. These physicochemical parameters may be used as tool in the quality control of herbal industry, thus adulteration may be avoided and the quality of herbal drug may be improved. Mahek et al. (2011) determined different physicochemical parameters. The ash values of the powdered *V. thapsus* leaf revealed a high concentration of total ash. The total ash, acid insoluble and water soluble ash substances were found to 14.32, 4.75, 8.30% w/w respectively in leaves. The ethanol and water soluble extractives are 11.87 and 6.51% w/w respectively. Loss on drying of the powdered *V. thapsus* leaf revealed the presence of 5.57% of moisture in a drug respectively. The average numerical values of stomatal number, stomatal index, vein islet number and vein termination number of lower surface of the leaves were found to be 96, 15.7, 14.5 and 12.5 (Mahek et al., 2011). Physicochemical characteristics of seed oil such as oxide stability index, refractive index and density were found 47.8 OSI (h), 1.4753 n₂₅ D, 0.933 respectively (Parry et al., 2006).

Ethnomedicinal uses of *Verbascum thapsus*

The *V. thapsus* is so widely distributed in the plant has various reported communities worldwide for various disorders of both humans and animals (Chart 1). The results indicate its traditional use is mostly confined to Latin-American countries, sub-continent and some European countries.

Pharmacological activities

There is resurgent interest in health benefits of herbs due to their diverse biological activities and pharmacological profile. The herbs exhibit these activities due to chemical constituents present in them. The momentous pharmacological activities of *V. thapsus* are cure and prevention of various diseases and improvement from diseases such as cancer, stroke and heart diseases.

Antioxidant activity

It is well-recognized that free-radicals containing oxygen and nitrogen species are responsible for various chronic diseases like Parkinson's and Alzheimer's diseases, atherosclerosis, aging, and cancer in biological systems. Various constituents present in plants like phenolic compounds, vitamin C, vitamin E, carotenoids and certain minerals, such as zinc and selenium are capable of neutralizing the effects of free radicals. Therefore due attention is being paid to the protective biochemical functions of naturally occurring antioxidants from plants. Antioxidant activity of alcoholic stem extract was investigated using DPPH assay, Table 1 (Kumar and Singh, 2011). Ethanolic extract of the plant resulted up to 85% inhibition of free radical and up to 40% inhibition by water extract in DPPH assay (Narayanaswamy and Balakrishnan, 2011). ORAC is a widely accepted measurement of free radical-scavenging capacity. ORAC values of the cold-pressed seed oil extracts were determined. Parsley, cardamom, and milk thistle seed oils exhibited ORAC values over 100 $\mu\text{mol TE/g}$ oil, whereas *V. thapsus*, onion, and roasted pumpkin seed oils had ORAC values less than 30 $\mu\text{mol TE/g}$ (Parry et al., 2006). Antioxidants differ in their free-radical quenching property due to their action at specific cell sites. This may explain different antioxidant effects observed by different biological assays.

Aqueous and ethanolic extract of whole plant had nice antioxidant activity inhibit sebum oxidation and thus prevent body smell and skin aging (Ota et al., 1999). Antioxidant activity of 35 plant species traditionally used for symptoms of diabetes or its complications were determined including root extract of *V. thapsus* using DPPH assay (IC₅₀ in ppm 67.80), NBT/XO assay (8.07% inhibition) and DCF/AAPH assay (10.31% inhibition) (McCune and Johns, 2002).

Pharmaceutical dosage forms, such as capsules, tablets, the dried form as in the tea, the 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; Kogje et al., 2010). It is suggested results from above that *Verbascum thapsus* is a rich source of antioxidants. Although studies exist on antioxidant activity of extracts, however no study is present on antioxidant activity of isolated compounds from this plant.

Wound-healing activity

Treatment of the coetaneous wound creation in rabbit with topical application of herbal extract of *Verbascum thapsus* was associated with enhanced formation of epidermis and deposition of connective tissue compared to control group animals. The results showed that *V. thapsus* extract 20% good healing effect on regeneration (Mehdinezhad et al., 2011). Bioactive compound responsible for this activity needs to be explored for commercial utilization as invention.

Chart 1Ethnomedicinal uses of *Verbascum thapsus* L.

Part used	Medicinal uses	Location	Reference
Whole plant	Remedy in the treatment of tuberculosis	Ireland	Allen and Hatfield, 2004
Leaves, flower	Skin diseases, cuts, wounds and swelling	Malakand, Pakistan	Sher, 2011
Whole plant	Ear problems of cats and dogs	Canada	Lans et al., 2008
Flower and leaves	Inflammatory ailments in respiratory tract and others	Mexico	Rodriguez-Fragoso et al., 2008
Aerial part	Wound healing, urinary disease, edema	Nepal	Rajbhandari et al., 2009
Flower	Respiratory tonic for ruminants	British Columbia	Lans et al., 2007
Leaves	Antitussive	Albania and Italy	Pieroni and Quave, 2005
Infusion from root	In combination for dental treatment	Medieval England	Anderson, 2004
Flower and leaves	Pulmonary disease, fever and bleeding of lungs and bowel	Pakistan	Shinwari and Gilani, 2003
Ointment, decoction in olive oil	Antitussive	Bulgaria	Leporatti and Ivancheva, 2003
Flower	Emollient against catarrh and coughs cataplasm applied externally to soothe gangrenous sores	Italy	Leporatti and Ivancheva, 2003
Flower	Topical inflammatory processes in humans and animals	Abruzzo (Italy)	Turker and Gurel, 2005
Olive oil extract of the leaves	Rectal prolapsed locally in veterinary medicine	Italy's Tuscany region	Manganelli et al., 2001
	Skin diseases, wound healing and gastrointestinal system ailments in sheep, mules, cattle and horses	Italy	Viegi et al., 2003
Roots	With <i>Allium sativum</i> for GI system in calves	Italy	Viegi et al., 2003
Roots	Treatment of the symptoms of diabetes and its complications	North American boreal forest, Canada	McCune and Johns, 2002
Flower and leaves	Diuretic, expectorant and sedative	Turkey	Dulger et al., 2002
Leaves Leaves in powdered form	Diarrhea and dysentery in cattle used for healing wounds and the seeds used as a fish poison	Islamabad, Pakistan	Shinwari and Khan, 2000
Oil from flower	For treatment of piles, bruises and frostbites	Germany	Grieve, 1981
Whole plant	Active against snake bite venom	Uttar Pradesh, India	Jain and Puri, 1984
Leaves	Ointments for burns and earache	Eastern United States	Houghton, 1978
Tea	For lung disease	ancient Rome and now in modern Ireland	DeBray, 1978
Dried flower or root	As cigarettes for asthmatics	Indians and Menominee (Michigan)	Lewis and Elvin-Lewis, 1977
Seeds	Used as a fish poison	Europe and Asia	Wilhelm, 1974

Table 1

Antioxidant activities expressed as IC₅₀ (Kumar and Singh, 2011).

Part used	Anti-oxidant activity (µg/ml)
leaf	> 100
stem	33.16
root	35.21

Antimicrobial activities

Plant-derived medicines have been a part of traditional healthcare in most parts of the world for thousands of years and there is increasing interest in the plants as the source of microbial agents to fight diseases (Zia-Ul-Haq et al., 2011). Khan et al evaluated methanol extract of aerial parts of *V. thapsus* against four gram-positive and five gram-negative bacteria five species *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Enterococcus faecalis*. Gram negative: *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Vibrio cholera* and *Enterobacter coccus*. They reported MIC value against *Vibrio cholera*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Escherichia coli* 10, 1, 1,1,12.5 and 15 mg/ml respectively but no activity was reported against *Micrococcus luteus*, *Enterococcus faecalis* and *Enterobacter coccus* (Khan et al., 2011).

Another antibacterial study was carried out on ethanol extract of *V. thapsus* stem against gram positive bacteria: *Bacillus subtilis*, *Staphylococcus aureus* and gram negative bacteria: *Escherichia coli* and *Pseudomonas aeruginosa*, Table 2, (Kumar and Singh, 2011).

Tucker and Camper studied in detail antibacterial activity using disc diffusion assay of common mullein (*V. thapsus*) extracts and commercial Mullein products. Six bacterial strains were used in the bioassay: *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *S. epidermidis*. The commercially obtained Mullein flower oil sample inhibited growth of all test organisms except *S. epidermidis* and *S. pyogenes*; the only other inhibitory activity was detected with the commercial alcohol extract against *K. pneumoniae*. Decoction from commercially

Table 2

Antibacterial activity expressed as Minimum Inhibitory Concentrations (Kumar and Singh, 2011).

Ethanol extracts	<i>B. subtilis</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
<i>V. thapsus</i> leaf	32	32	32	> 250
<i>V. thapsus</i> stem	8	16	32	> 250
<i>V. thapsus</i> root	32	128	> 250	32

obtained leaf material was inhibitory to all test organisms except *P. aeruginosa* and *S. pyogenes*. Only *K. pneumoniae* was inhibited by the Mullein tea sample. This activity was attributed to the saponins (Meurer-Grimes et al., 1996; Speranza et al., 2010).

Sandra et al evaluated forty-three plant species for *in vitro* antimycobacterial activities including the flower and leaf of *V. thapsus*. The MIC value (µg/ml) against *M. aurum* > 500 *M. smegmatis* > 500 were reported (Sandra et al., 2002). Mullein herb was also reported in other study for anti-tubercular positive results during clinical trials (Carthy and Mahony, 2011).

The *V. thapsus* methanol extract of aerial parts was studied against *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus fumigatus* and *Rhizoctonia solani* using agar tube dilution method their linear percent inhibition were determined to be 25.53, 58.39, 23.18 and 64.09 respectively (Khan et al., 2011). The broad spectrum antimicrobial potential of this species suggests it a potential candidate as antimicrobial agent and should be explored for antimicrobial lead entities. The results indicated that Gram positive were more susceptible than Gram negative bacteria. Gram-positive bacteria are usually more sensitive to crude extracts and bioactive constituents because of the specific structure of their cell walls (Zia-Ul-Haq et al., 2013).

Antiviral activity

Investigation was for *in vitro* antiviral activity against Herpes simplex virus type 1 (HSV-1) and influenza virus A by dye uptake assay systems HSV-1/Vero in the cells and influenza virus A/MDCK cells. *V. thapsus* exhibited strong anti-influenza virus activity with IC₅₀ < 6.25 mg/ml (Rajbhandari et al., 2009). In another study, one hundred methanolic plant extracts were screened for antiviral activity against their 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). The antiviral effect was strongest noted with decoctions of *V. thapsus* flowers (Skwarek, 1979). Zanon et al. (2002) investigated the alcoholic extracts of several species including *Verbascum thapsus* in Vero cells-pseudorabies virus strain RC/79 (herpes virus suis) system the alcoholic extract of *V. thapsus* were able to inhibit at least 2 log, the viral infectivity. Maximum non-cytotoxic concentration was determined 1.40 mg per ml plant materials. An antiviral agent is known due to its potential of being non-toxic for the host cell, so that the inhibition observed should only be due to a direct action in the viral replication. Based on above observations, *V. thapsus* might be further explored for its antiviral indications. Since anti-viral synthetic medicines are costly therefore the chemical entity responsible for this activity present in crude extract of common mullein should be isolated, purified, characterized and clinical trial should be performed for potential commercial use.

Anticancer and cytotoxic activity

Verbascum thapsus was evaluated for its anti-hepatoma activity on five human liver-cancer cell lines, i.e. HepG2/C3A,

SK-HEP-1, HA22T/VGH, Hep3B and PLC/PRF/5. The hot water extract of crude drug was examined by *in vitro* evaluation for its cytotoxicity. The results showed that the effect of crude drug on hepatitis B virus genome-containing cell lines were different from non those against hepatitis B virus genome-containing cell lines. The inhibitions at 2000 µg/ml dose were 31% (HepG2/C3A), 69.9% (HA22T/VGH) and 11.6% (PLC/PRF/5) on HBV (-) and HBV (+) cell lines. *V. thapsus* was observed to be potent effective against the growth of three cell lines (Lin et al., 2002). Aqueous extract and alcoholic extract of *V. thapsus* anti-cancer resulted *in vitro* enzyme MMP-9 and Cathepsin B inhibition assay (Cyr, 2010).

Turker and Camper studied biological activity of common mullein extracts (water, ethanol, methanol) and commercial Mullein products using selected bioassays, antitumor and two toxicity assays (brine shrimp and radish seed). *Agrobacterium tumefaciens*-induced tumors in potato disc tissue were inhibited by all extracts. Toxicity to brine shrimp and radish seed germination and growth was observed at higher concentrations of the extracts (Speranza et al., 2010). The compound 3,5-dihydroxy-6,7-dimethoxy flavone, useful as an antiasthmatic and antiallergic was 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). Follow-up studies should be performed to identify the responsible bioactive principle and to determine the anticancer mechanism of action.

Antihyperlipidemic activity

Studied antihyperlipidemic activity was induced in rats with hyperlipidemia, polysaccharides obtained from the leaves of *V. thapsus* exhibited significant decrease in the cholesterol and triglyceride levels (Aboutabl et al., 1999). Hyperlipidemia plays a major role in the development of coronary heart diseases, atherosclerosis, obesity, hypertension and diabetes mellitus which are the major causes of mortality worldwide. The study suggests its potential commercial use as antihyperlipidemic agent. The mechanism by which *V. thapsus* exerts antihyperlipidemic effects still needs attention of researchers.

Antigermination activity

Pardo et al. (1998) investigated phytotoxins from an ethanolic extract of 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 and formulations

Leaves of *V. thapsus* part of hair tonic that inhibit 5- α -reductase and stimulate hair outer root sheath proliferation, so used as hair tonics (Ito et al., 2007). Mullein-tops (*V. thapsus*) along with other plants are intended especially for the treatment of consumption, asthma, and hemorrhages (Nichols, 1887). Another invention contain *Verbascum* one of its constituent for the therapy of ear diseases (Nakar, 2004). *V. thapsus* extract was in the formulation was used to treat skin disorders by

applying affected areas of the skin twice daily (Williams, 1997). It is reported to be a part of polyherbal formulation of cosmetics, bath preparations and detergents that showed skin moisturizing and conditioning effects (Ohara et al., 2001). Naturopathic Herbal Extract Ear Drops (NHED, including *V. thapsus*) may be beneficial in Otitis media that is one of the most frequent diseases of early infancy and childhood (Sarrell et al., 2003). *V. thapsus* was mentioned in the composition of healing plaster for all bodily disorders such as strains, bruises, fresh wounds, inflammation, rheumatic, neuralgic, chronic pains and ulcerations (Baker, 1885). Another formulation made by Humphrey from Iodine and mullein in combination for throat disease (Humphrey, 1869). *V. thapsus*, an algae, *Medicago sativa*, and *Symphytum officinale*, together with other optional components resulted the formulation for use as a tobacco substitute and as an aid in the cessation of tobacco use. The invention is an important substitute tobacco in cigarettes or pipes that produce diminished desire for tobacco (Coy-Herbert, 2002). The extract prepared from *V. thapsus* demonstrated ability to inhibit its one or more extracellular proteases, which degrade human tissue matrix (Cyr, 2002) this inhibitory activity can be used to minimize during protein purification due to the degradation extracellular proteases. Tincture made from dried leaves promote healthy hair in baldness and dandruff preparations (Roia, 1966).

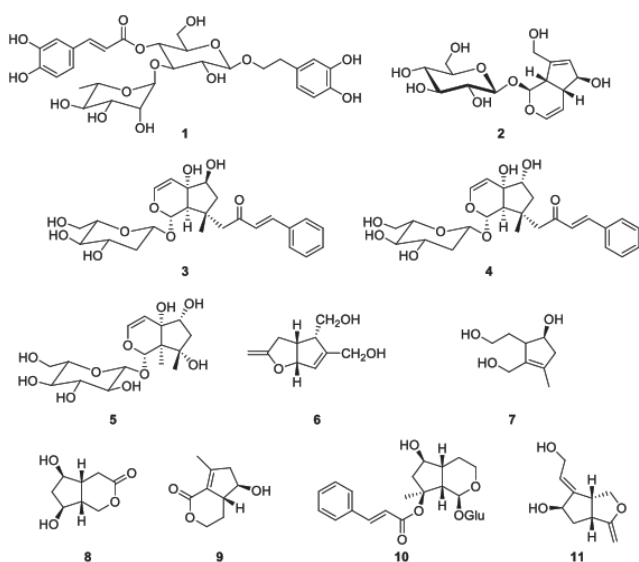
Phytochemistry

The great diversity of chemical classes is found in *V. thapsus*, mainly glycosides, flavonoids, saponins and terpenoids. The potential therapeutic implications of common mullein are due to these bioactive constituents however detailed mechanisms of the various activities describing structure-activity relationship still require intensive investigation. *In-vitro* and *in-vivo* studies describing toxicity and safety and efficacy studies suggesting optimal dosage for human consumption for cure of various diseases of these bioactive constituents should be performed to rationalize its uses folk-lore for cure of various ailments.

Iridoid glycosides

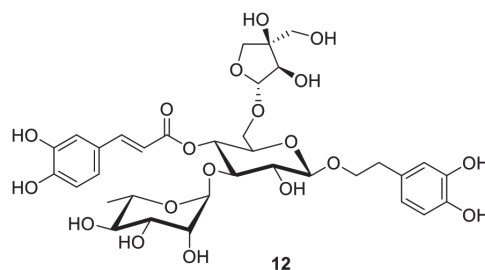
Verbascoside (**1**) was one of the earliest iridoid glycoside reported from the leaves of *V. thapsus* (Murakami, 1940). Aucubin (**2**) was obtained in greater quantity in roots compare to aerial parts (Groeger and Simchen, 1967). Pardo et al. (1998) isolated iridoid glucosides laterioside (**3**), harpagoside (**4**), ajugol, and aucubin from an ethanolic extract of the roots of *V. thapsus* that showed antigermination activity on seeds of barley (*Hordeum vulgare*). Aucubin, isocatalpol, methylcatalpol, and 6-O- α -L-rhamnopyranosylcatalpol were reported by Seifert et al. (1984). Warashina et al. worked on whole plant of *V. thapsus* and isolated various iridoids e.g. saccatoside, 6-O-(3"-O-p-coumaroyl)- α -L-rhamnopyranosylcatalpol, 6-O-(4"-O-p-coumaroyl)- α -L-rhamnopyranosylcatalpol, 6-O-(2"-O-(p-methoxy-trans-cinnamoyl)- α -L-rhamnopyranosylcatalpol, 6-O-(3"-O-(p-methoxy-trans-cinnamoyl)- α -L-

rhamnopyranosylcatalpol, verbascoside A, 6-O-[2''-O-(3,4-dihydroxy-trans-cinnamoyl)]- α -L-rhamnopyranosyl catalpol, 6-O-[4''-O-(3,4-dihydroxy-trans-cinnamoyl)]- α -L-rhamnopyranosylcatalpol, 6-O-[3''-O-(3,4-dimethoxy-trans-cinnamoyl)]- α -L-rhamnopyranosylcatalpol, 6-O-(2''-O-feruloyl)- α -L-rhamnopyranosylcatalpol, 6-O-(4''-O-feruloyl)- α -L-rhamnopyranosylcatalpol, 6-O-(2''-O-isoferuloyl)- α -L-rhamnopyranosylcatalpol, 6-O-(3''-O-isoferuloyl)- α -L-rhamnopyranosylcatalpol, and 6-O-(4''-O-isoferuloyl)- α -L-rhamnopyranosylcatalpol (Warashina et al., 1991). Harpagide (5) from aerial parts (Bianco et al., 1980) while 5-O- α -L-rhamnopyranosyl (1 α -3)-[α -D-glucuronopyranosyl (1 α -6)]- α -D-glucopyranoside was reported from whole plant (Mehrotra et al., 1989). The most recent isolation studies by Zhao et al. (2011) resulted ajugol, ningpogenin (6), 10-deoxyeucommiol (7), jioglutolide (8), 6- β -hydroxy-2-oxabicyclo [4.3.0] Δ 8-9-nonen-1-one (9), 8-cinnamoylmyoporoside (10) and verbathasin A (11) from aerial parts of *V. thapsus*.



Phenylethanoid glycosides

Warashina et al. isolated phenylethanoid glycosides from *V. thapsus* e.g. forsythoside B (12), alyssonoside, arenarioside, 1'-O- β -D-(3,4-dihydroxy-phenyl)-ethyl- α -L-rhamnopyranosyl-(1 \rightarrow 3')- β -D-xylopyranosyl-(1 \rightarrow 6')-4'-O-feruloyl-glucopyranoside, leucosceptoside B, 1'-O- β -D-(3-hydroxy-4-methoxy-phenyl)-ethyl- α -L-rhamnopyranosyl-(1 \rightarrow 3')- β -D-xylopyranosyl-(1 \rightarrow 6')-4'-O-feruloyl-glucopyranoside, cistanoside B and 1'-O- β -D-(3,4-dihydroxy-phenyl)-ethyl- α -L-rhamnopyranosyl-(1 \rightarrow 3')-3''-hydroxy-4'''-O- β -D-glucopyranosyl-cinnamoyl-(1 \rightarrow 6')-glucopyranoside (Warashina et al., 1992). Later another group isolated ergosterol peroxide, docosanoic acid, oleanolic acid and β -sitosterol from the flowers of *V. thapsus* (Zhang et al., 1996).



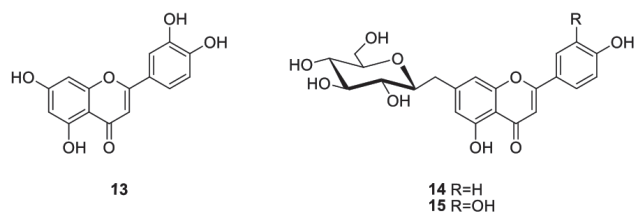
Terpenes

The structural diversity of the terpenes is reflected in their different pharmacological properties. Hussain et al. (2009) isolated two sesquiterpenes: buddindeterpene A and B; one diterpene i.e. buddindeterpene C from whole plant of *V. thapsus* collected from northern area of Pakistan.

Flavonoids and carotenoids

Flavonoids are getting reputation due to their antioxidative and anticancer activities besides their role in managing oxidative stress in biological systems due to their ability to act as free radical scavengers and quenchers of singlet oxygen formation. Kogjeet et al. (2010) determined phenolic and flavonoid content *V. thapsus* various parts, total phenolic content of leaf 0.124, stem 0.166, root 0.100 (mg/g dry weight) and total flavonoid content leaf 0.024, stem 0.009, root 0.018 (mg/g dry weight).

Danchul et al. (2007) studied the composition of flavonoids of 22 species in genus *Verbascum*. Underground parts and aerial parts of plants including stems, leaves, flowers and seeds were investigated. Six flavonoid compounds acacetin-7-O- α -D-glucoside, luteolin (13), cynaroside (14), kaempferol, quercetin, and rutin were isolated and characterized. From the 70% aqueous acetone extract of dry aerial parts of *V. thapsus* a flavonoid apigetrin (15) was isolated (Zhao et al., 2011).



The new flavonoid, 4',7-dihydroxyflavone-4'-rhamnoside, was isolated and identified by usual methods from the leaves and flowers of *V. thapsus*, together with 6-hydroxyluteolin-7-glucoside and 3'-methylquercetin (Souleles and Geronikaki, 1989). Mullein seed oils contain carotenoids that may serve as dietary sources, especially zeaxanthin (Parry et al., 2006).

Parry et al. studied composition of the mullein seed oil along with other food oil. It was found that mullein seed oils had relatively higher γ -tocopherol levels with a ratio of 1:10 for α - to γ -isomers. Mullein seed oil contained the highest level of δ -tocopherol among all tested seed oils; and the lowest δ -tocopherol content. In summary, the cold-pressed seed

oils may mullein serve the dietary sources for γ -tocopherol. The cold-pressed seed oil mullein may also provide dietary δ -tocopherol (Parry et al., 2006) as shown in Table 3.

Table 3
Carotenoid contents in the cold-pressed seed oils.

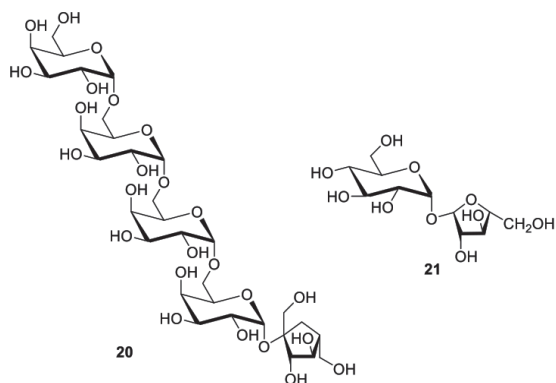
Carotenoid	Contents
β -carotene	1121.00 ($\mu\text{g}/\text{kg}$)
lutein	62.10 ($\mu\text{g}/\text{kg}$)
zeaxanthin	6.40 (mg/kg)
cryptoxanthin	1.30 (mg/kg)
Total carotenoids	15.80 ($\mu\text{mol}/\text{kg}$)

Saponins

Saponins are an important phytoconstituent ascribed to various biological actions like antimicrobial, antileishmanial, antiplasmodial, antimalarial, antitumoral and antiviral activities. Saponins reported from *V. thapsus* are given in Chart 2. It may be concluded that various antimicrobial, antiviral and antitumoral activities of *V. thapsus* may be due to these constituents.

Chart 2
Chemical constituents reported from *V. thapsus*.

Saponins	Plant parts	Reference
triterpene A (16)	Aerial parts	Pascual Teresa et al., 1978a,b
triterpene B (17)		
saikogenin A (18)		
veratric acid (19)	Benzene extract	Pascual Teresa et al., 1978a,b
β -spinasterol	Aerial parts	Bianco et al., 1980
6-O- β -D-xylopyranosyl aucubin		
thapsuine B		
hydroxythapsuine	Aerial parts	Pascual Teresa et al., 1980
thapsuine A	Aerial parts	Zhao et al., 2011
hydroxythapsuine A		
3-O-fucopyranosylsaikogenin F		



Carbohydrates

Carbohydrates are the most abundant biomolecules and may be found as free monosaccharides, oligosaccharides, polysaccharides, or as glycoconjugates, like glycoproteins, glycopeptides, glycolipids and glycosylated natural products. Various carbohydrates reported from different parts are presented in Chart 3.

Chart 3

Fatty acids compositions of the studied cold-pressed seed oils (Parry et al., 2006).

Carbohydrates	Plant parts	Reference
Verbascose (20)	Roots	Murakami, 1940
stachyose	Roots	Hattori and Hatanaka, 1958
heptaose		
octaose		
nonaose	Trichomic cells	Miroslavov and Komarov, 1959
sugars	Ethanol extract	Pascual Teresa et al., 1978b
Sucrose (21)		
Pectins	Roots	Verdon, 1912

Minerals

Presence of various minerals up to an acceptable limit is essential for the normal physiological and biochemical functions human. Pande and Tewari analyzed the ash of *V. thapsus* is both acidic and basic radicals in detail (Chart 4) (Pande and Tewari, 1960). However Cr and Ni were found in anomalous concentration in *V. thapsus* that can be a major environmental threat with regard to the health of the inhabitants of the area (Kfayatullah et al., 2001). Similarly the plant was reported for high scavenging ability for Zn and Pb from the soil that could cause serious environmental and health problems in the area of the living organisms (Shah et al., 2004). Usually presence of minerals in plants depends on cultivars, agrogeoclimatological conditions of area from where plant parts were collected, maturity and collection time of plant parts, chemical composition of soil, water and fertilizers applied as well as permissibility and selectivity of minerals during uptake of water by plants.

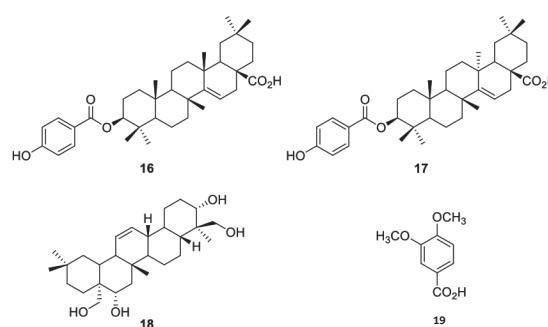


Chart 4Minerals reported from *V. thapsus*.

Elements and radicals	Plant part	Reference
Basic elements	Ash of fruit	Pande and Tewari, 1960
Al		
Na		
K		
Mg		
Acidic radicals		
carbonate		
sulfate		
chloride		
silicate		
Cr and Ni	Whole plant	Kfayatullah et al., 2001
Zn and Pb	Whole plant	Shah et al., 2004

Lipids

V. thapsus seed oils had high total poly unsaturated fatty acid (PUFA) contents (Table 4), with linoleic acid (18:2n-6) as the primary fatty acid. The biomechanical functions of PUFA are currently under extensive research including their influence/impact on cellular signaling and membrane structure; gene expression and prostaglandin biosynthesis; and nervous, endocrine, and immune system mediations (Yehuda, 2001; Parry et al., 2006).

Petrichenko and Razumovskaya (2004) explored the compositions of fatty acids in seeds of *V. thapsus*. The seeds contain 29-33% of oil that had eleven fatty acids among

Table 4

Fatty acids compositions of the studied cold-pressed seed oils (Parry et al., 2006).

Fatty acid	<i>V. thapsus</i> (g/100 g oil)
14:0	TR
16:0	6.0
16:1	0.1
18:0	2.7
18:1	16.1
18:2	73.1
18:3	1.0
20:0	0.7
20:1	0.2
SAT	9.4
MUFA	16.4
PUFA	74.2

TR, trace; SAT, total saturated FA (g/100 g oil); MUFA, total monounsaturated FA (g/100 g oil); PUFA, total polyunsaturated FA (g/100 g oil).

unsaturated fatty acids up to 88-90% linoleic and oleic acid dominated. They found that the distribution of the chemical elements increases towards the apex in *V. thapsus* (Petrichenko and Yagontseva, 2006). Detailed compositions of fatty acid are given in Table 5. Pascual Teresa et al. (1978a,b) isolated palmitic, stearic, oleic, linoleic, linolenic, arachidic, and behenic acids and β -sitosterol from benzene extract of seed oil of *V. thapsus* and ergosta-7-en-3 β -ol from the nonsaponifiable fraction. Pande and Tewari reported that fat petroleum ether extract of *V. thapsus* contained the esters of: stearic acid 16.4, palmitic acid 30.96, oleic acid 29.2, and linoleic acid 4.8% (Pande and Tewari, 1960). Since various factor like plant variety, maturity stage of collection of seeds and agro-geo-climatic condition of area from where seeds are collected affect oil content and composition so there is need to collect at-least three year data with controlled conditions to establish themselves in reliable database oil composition of this species.

Table 5

Tocopherol contents in the cold-pressed seed oils (Parry et al., 2006).

Tocopherols	<i>V. thapsus</i> (mg/kg)
α -tocopherol	27.1
γ -tocopherol	213.3
δ -tocopherol	76.2
Total tocopherols	759.4 (μ mol/kg)

Miscellaneous compounds

Peroxidase, ascorbic acid and tannins were confirmed in trichomic cells (Miroslavov and Komarov, 1959), α -galactosidase in roots (Bom and Van, 1998) androtenone in leaves of *V. thapsus* (Obdulio and Lobete, 1943). The flavone compound was isolated from hexane extracts of *V. thapsus* which had antiasthmatic and antiallergic effects (Kawamo et al., 1988). Ahmad et al (2005) reported (+)-genipin, α -gardiol and β -gardiol.

Conclusion

The information presented in this review shows the potential pharmacological importance of *V. thapsus* and its role in improving health. It is an important source of minerals and vitamins and health-promoting fatty acids. The presence of glycosides and saponins and broad spectrum pharmacological activities indicates the potential of this species for the treatment of various chronic diseases and highlights the need for well-designed clinical trials to rationalize the traditional uses. There is a dire need to isolate and identify new compounds from different parts of the plant, which have possible antitumor and antihyperlipidemic properties.

Authors contributions

MR and MZUH searched literature from various databases and organized the manuscript. HZEJ critically read, refined and formatted the manuscript. All authors read and approved the final manuscript for publication.

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