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AN OVERVIEW OF THERAPEUTIC POTENTIALS OF *TARAXACUM OFFICINALE* (DANDELION): A TRADITIONALLY VALUABLE HERB WITH A REACH HISTORICAL BACKGROUND

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Abstract – Taraxacum officinale *or dandelion* (Asteraceae or Compositae family)*, is an edible plant spread worldwide. It has been believed that dandelion originated in Greece, or perhaps the Northern Himalayas, and spread across temperate areas to Europe and Asia Minor. Dandelion is widely used worldwide in food products. It is traditionally proposed as a dietary supplement and herbal remedy for the prevention, management, and treatment of various human diseases. This review intended to investigate the pharmacological and therapeutic features of dandelion in traditional medicine and scientific documents. Results from several studies indicated that this plant owned numerous biological potencies, including anti-inflammatory, anti-tumor, immunostimulatory, anti-microbial, anti-viral, anti-oxidant, anti-diabetic, geno-protective, diuretic and kidney-protective, hepato-protective, neuro-protective, anti-depressant, lung-protective, pancreas-protective, and differentiation-inducing actions as well as exerting a positive influence on dyslipidemia, hematological profile, stomach motility, fatigue, and bifidobacteria. Nevertheless, the exact mechanism of action for these features is not fully understood. All the studies done on dandelion involved experimental animal studies as well as some human studies and cell cultures, and no clinical data are available for the claimed benefits in the prevention and treatment/management of diseases. Available published data about animal and human studies, both* in vitro *and* in vivo *showed great potentials for the use of dandelion as therapy in most diseases. For such a ubiquitous herb, well-designed human studies are surprisingly rare. Due to the lack of toxicity and side effects, this plant has been considered as a worthwhile complementary drug. Further clinical trials are required to validate the reported promising experimental effects in clinical use. Here we reviewed the studies that validated the efficacy of dandelion claimed by traditional healers.*

KEYWORDS: Taraxacum officinale*, Dandelion, Medicinal plant, Anti-oxidant, Anti-cancer, Anti-diabetes*

INTRODUCTION

The application of herbal medicine for the treatment of various diseases is as old as mankind. According to fossil records, the human use of plants in the prophylactic or curative scopes may be traced back at least 60,000 years ago. In ancient times and Middle Ages, the plants were considered the only medicines for the treatment of illnesses, because at that time they thought that the

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bodies were adapted with those substances which nature provides for the benefit of living creatures. Herbs are also used in Iranian traditional medicine[1]. The historical sources relevant to the medicinal plants' use were reviewed by Petrovska[2].

Today, plants have been utilized worldwide as a source of medicine by people from all cultures and traditional medicine is an important part of the health care system in most nations. The recent increasing concern in herbal remedies has been associated with several factors including better cultural acceptability, better compatibility with the human body, their safety, lower economical cost, effective, easy availability, and fewer side effects as compared to orthodox drugs[3]. The World Health Organization (WHO) supports the use of traditional medicine, provided they are proven to be efficacious and safe (WHO 1985). Today, it has been estimated that 25% of drugs are directly or indirectly from plant origin[4].

Plants of the genus Taraxacum belongs to the family Asteraceae or Compositae (also referred to as the aster, daisy, or sunflower family), subfamily Cichorioideae, tribe Lactuceae, have long been accepted as medicinal herbs. The first reference to its application is reflected in its name, which is derived from the Greek words "taraxis" for inflammation and "akeomai" for curative[5]. Taraxacum officinale, commonly named dandelion, is an edible plant spread worldwide[6]. The common name for dandelion is an alteration of "dent de lion", a phrase thought to be based on the Welsh "Dant y Llew" of the thirteenth century, meaning "tooth of the lion". This name maybe because of the form of the young seeds, the jagged form of the leaves, the appearance of the yellow florets of the inflorescence, or the strong white taproot (pulling it from a lawn is like trying to extract a lion's tooth). Its French name, pissenlit, is attributed to the diuretic activity of the plant parts[7]. As discussed later, it was proposed in traditional medicine for several kinds of human ailments and disorders. It has a very reach historical background, exhibited a wide spectrum of pharmacological potentials.

HISTORY AND DISTRIBUTION

The first scientific classification of dandelion was by Linnaeus in 1753 as Leontodon taraxacum. Wiggers (1746–1811) explained the genus Taraxacum, and Georg Heinrich Weber created the current classification in 1780. Many botanists consider that dandelion originated in Greece, or perhaps the Northern Himalayas, and spread across temperate areas to Europe and Asia Minor. Dandelion has a fossil record that goes back to glacial and interglacial times in Europe and it is believed to have colonized the Americas post-Pleistocene via Beringia. Later introductions of this plant to North America are obscured in opposing claims. It may arrive on the east coast with the Vikings about 1000 AD, or it first came on the Mayflower, or the introduction was by later settlers who brought it as a garden plant or a pot herb for medicinal purposes. The earliest recorded observation of dandelion in North America was in the New England area in 1672. The Cree, Digger, Apache, and Mohican Indians soon became aware of its properties and used it as a medicinal herb. There have likely been multiple introductions from many sources. The plant is assumed to have spread to the west coast with loggers and settlers. The first Canadian collection of dandelion was made in Montréal, QC, in 1821, where it was observed as a common species. Now it is widely spread through Europe, Asia, and America[8].

It blossoms almost the whole year. It starts growing in the autumn and is seen in parks, pastures, meadows, fields, lawns gardens, wildlands on disturbed banks, shores of waterways, waste ground, and by the roadsides, at altitudes ranging from sea level to two thousand meters with moist soils. It is so abundant that farmers everywhere find it a troublesome weed[7-9].

HERB MORPHOLOGY

Dandelion is a perennial weed producing a sturdy taproot, which reaches an average length of 15-30 cm with 2 to 3 cm wide. Nevertheless, roots 60-100 cm in length are also found. It is fleshy and brittle and is dark brown on the outside, white and milky inside. The roots can produce new plants even when the plant is cut at or below the soil surface. The large, long, polished, hairless, and light to dark green leaves (5-40 cm long and 1–10 cm wide) are gathered in a rosette at the bottom of the plant and are deeply serrated at ground level. Leaves grow from the highest end of the root at ground level, and it has a short stem. The leaves are organized in a rose-like manner. They are of different kinds: with dental borders, with almost complete borders, some of them have deep dental borders which end in the central nervation. The flowering stalks are upstanding, 5-40 cm long, and carrying a solitary, terminal inflorescence. Leafless hollow stems, which emerge from the center of the rosette. It has single, golden yellow flowers on straight. On average, each plant is developing 5-10 flowers. The fluorescence ranges from 7 to 15 mm in diameter and is composed of 140-400 yellow, ligulate florets. Flowers are produced from early spring until late autumn. When the florets ripen, they create downy seeds, which are easily scattered by the wind. The fruits are conical achenes, brown and crowned by a white, hairy pappus, which allows the seeds to be distributed by wind. The fruit is cotton-like with many seeds[10-12] (Figure 1).

Fig. 1. *A*, Dandelion herb, *B*, its flower, and *C*, ripe fruits.

CHEMICAL COMPOSITION

Considering the great history of the dandelion in herbal medicine, relatively little is known about the chemical constituents. Newly cDNA of the synthetic enzyme of triterpenes from this herb was introduced, which are responsible for the annelation reaction of oxido-squarens. So, here could still exist novel triterpenes in the plants of Taraxacum species[13]. The harvest time influenced the amounts of phytocompounds in dandelion. The most suitable period for plant collection from its natural environments is depended on its targeting medical applications[14]. The dandelion root is a rich source of inulin: about 2% in the spring, increasing to about 40% in fall. As in the roots, the dandelion leaves contain sesquiterpenes as well as p-hydroxyphenylacetic acid and b-sitosterol. The most abundant phenolic compounds in the leaves and flowers are hydroxycinnamic acid derivatives, in particular caffeic acid esters such as chlorogenic, chicoric and monocaffeoyltartaric acids. Compared to the roots, the dandelion leaves are characterized by higher polyphenol contents[15]. It also is a rich source of a variety of vitamins and minerals, including beta carotene, nonprovitamin A, carotenoids, xanthophylls, chlorophyll, vitamins C and D, many of the B-complex vitamins, choline, as well as minerals iron, silicon, magnesium, sodium, zinc, manganese, copper, and phosphorous[7,16]. Sesquiterpene lactones confer a bitter taste to the plant, which is particularly notable in the Leaves but also in the roots especially when spring-harvested. Saponins, flavonoids, alkaloids, phenols were very concentrated in the stem, root, and flower, with a higher concentration of flavonoids in the flower extracts. Phenols and steroids were also found in the investigated plant parts[17]. The phytochemicals presented in dandelion, their structure and biological significance are listed in Supplementary Table 1.

TABLE 1. Traditional uses of dandelion in various countries around the world.

NO.	Vernacular name	Country	Traditional uses	Refs.
1	Löwenzahn	Germany	To medicate gout, diarrhea, blister, spleen and liver complaints	5
2	Blowballs	America	To remedy kidney disease, dyspepsia and heartburn To be a "blood purifier" and is employed as a mild laxative, for treating arthritic and rheumatic complaints as well as eczema and other skin conditions	5
3	Diente de león	Mexico	To control diabetes mellitus and bacterial infection	5
4	Cırtlık	Turkey	As a laxative, diuretic and potent anti-diabetic medicine	5
5	蒲公英	China	To upper respiratory tract infections, bronchitis or pneumonia, and as a compress for its anti-mastopathy activity	5
6	Yanrin	Nigeria	Remedy against several ailments of liver dysfunction, diabetes and anti-inflammatory conditions	5
7	Dudhal or Kanphul	India	As a hepatic stimulant, diuretic, for liver disorders, and most interestingly, for chronic skin diseases	5
8	الهندباء	Arabic countries	To remedy liver and spleen disorders, whereas European herbalists authorize the use of dandelions for fever, boils, eye problems, diabetes and diarrhea	5
9	کاصدق	Iran	Liver and kidney diseases	13

NUTRITIONAL USES

The well-known pharmacological effects, together with the low toxicity make this herb a good candidate for use as a food source. Apart from being used as pharmaceutical, dandelion flowers, leaves and roots are processed into different food products. It is often marketed as a health food due to its history as a medicinal plant used to alleviate symptoms having diuretic, choleretic and laxative properties. Leaves of cultivated or wild species are consumed fresh as salad. A tea made from the leaves is laxative. They are often used to add flavor to salads, sandwiches, and teas. The roots (Taraxaci radix) are roasted and utilized as a coffee substituted. Its roots are processed into pharmaceutical preparations such as teas, tinctures, capsules, tablets and juices. Additionally, extracts are used as flavor components in various food products, including alcoholic beverages and soft drinks, frozen dairy desserts, candy, baked goods, gelatins and puddings and cheese. In the modern herbal medicine, all aforementioned functions of dandelion have been upheld, and the dried leaves, flowers and roots, and extracts are sold today as herbal teas, syrup and in the capsule form. The flowers are used to make certain wines. Dandelion salad is often accompanied with hard boiled eggs[5, 11, 38-41]. As mentioned before the results of studies indicated a nutritive potential for dandelion leaves; therefore, use in fresh salad is encouraged along with the local promotion and production of underexploited autochthonous plants, as suggested by the Food and Agriculture Organization, with the purpose of improving the nutritional condition of areas of population with poor economic resources[9].

DANDELION IN TRADITIONAL MEDICINE

In the traditional system of medicine, all parts of dandelion particularly the roots, are slightly aperient, cholagogue, depurative, powerfully diuretic, hepatic, laxative, stomachic, and tonic. The first confirmation for the therapeutic use of dandelion was quoted by Arabian physicians of the 10th and 11th centuries to treat liver and spleen diseases[5]. Traditional uses of dandelion in various countries throughout the world are presented in Table 1.

THERAPEUTICAL POTENTIALS

All the studies performed on dandelion involved experimental animal studies as well as some human studies and cell cultures, and no clinical data are available for the claimed benefits of dandelion in the prevention and treatment/management of diseases. Available published data about animal and human studies, both *in vitro* and *in vivo* showed great potential for the use of dandelion as therapy for some diseases. For such a ubiquitous herb, well-designed human studies are surprisingly rare. Nevertheless, numerous *in vitro* and *in vivo* assays have confirmed its therapeutic potentials supporting the long history of dandelion as a folk medicine[42, 6]. The dandelion root or the whole plant gathered while or before flowering, from both wild and cultivated plants, is utilized in studies[17]. The toxicity of dandelion was found to be low, due to the absence of any significant toxins. In mice, herb and root extracts administered intraperitoneally showed the median lethal dose (LD50) of 28.8 and 36.6 g/kg body weight, respectively[43]. Here we reviewed the studies that validated the efficacy of dandelion claimed by traditional healers.

ANTI-MICROBIAL ACTIVITY

The increased incidence of bacteria resistance to many anti-bacterial drugs is of great concern and medicinal plants have confirmed as an alternative source of anti-bacterial agents. In the attention of many researchers is the anti-bacterial potential of various plants[44]. Extraction and use of synthetic as well as inorganic anti-biotics are costly and pose a serious threat to health and environment; this has shifted attention to the use of traditional herbal drugs. Evidence showed that plant extracts had target sites different from those used by anti-biotics and will be active against drug-resistant microbial pathogens[45]. The anti-bacterial activity of various extracts of different parts of dandelion was examined (Table 2). It appears that the kind of solvents affected the anti-bacterial activity of dandelion because they could extract the different bio-organics differing in number and anti-microbial potentials. Dandelion also has good anti-microbial activity against dental pathogens and can be suggested as a useful herb to control dental caries and endodontic infections. It can be better drug candidates to combine with regular anti-microbial agents[46].

ANTI-VIRAL ACTIVITY

Viruses are responsible for a large number of human disorders. Several hard-to-cure illnesses and complex syndromes including Alzheimer's disease, type 1 diabetes, and hepato-cellular carcinoma have been connected with viral infections.

TABLE 2. *In vitro* anti-microbial activity of dandelion.

No.	Active constituents / preparations	Parts of plant	Micro-organisms	Results	Refs.
1	Ethanol and water extracts	Leaves	Escherichia coli, Klebsiella pneumoneae, Pseudomonas auregenosa and Staphylococcus aureus.	The anti-bacterial activity of both extracts was concentration dependent Ethanol extract was the most active compared with the water extract Of the bacteria tested, Escherichia coli was the most susceptible to the extracts	45
2	Water-soluble poly-saccharides extracted from the dandelion	Shoots	Escherichia coli, Bacillus subtilis and Staphylococcus aureus	High anti-bacterial activity at a concentration of 100 mg/mL	47
3	Ethyl acetate extract	Leaves	Aeromonas hydrophila, Salmonella typhi, Staphylococcus aureus, Bacillus cereus, Escherichia coli	Bacillus cereus was the most sensitive and Aeromonas hydrophila was the most resistance to the extract	48
4	Hydro-alcoholic extract	Leaves	Staphylococcus aureus, Escherichia coli and Salmonella abony entrica	Anti-microbial activity against Escherichia coli and Salmonella abony Lack anti-microbial activity against Staphylococcus aureus	44
5	Methanol, chloroform and distill water extracts	Leaves	Micrococcus luteus, Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli, and Staphylococcus aureus	The methanol and chloroform extracts were effective against all the tested bacterial pathogens Water extract showed no activity	49
6	Crude methanol hydrophobic and dialyzed extracts	Roots	Staphylococcus aureus,methicillin-resistant Staphylococcus aureus, Bacillus cereus, Escherichia coli and Salmonella typhimurium	The crude extract demonstrated the strongest inhibition of microbial growth against Staphylococcus aureus, methicillin-resistant Staphylococcus aureus and Bacillus cereus strains Normal phase (NP) fractionation of crud extract resulted in two fractions (NPF4 and NPF5) with enhanced anti-microbial activity. NP fractionation of NPF4 resulted in two fractions (NPF403 and NPF406) with increased anti-microbial activity	50
7	Dichloromethane, ethyl acetate, methanol and water extracts	Stems, roots and flowers	Streptococcus mutans, Streptococcus pyogenes, Streptococcus pneumonia, Streptococcus aureus and Pseudomonas aeruginosa	The extracts gave the varying values of inhibition against the microorganisms The concentration increases of the extracts resulted in the increase in the anti-microbial activities The methanol extracts had the highest anti-microbial potential against the all bacterial strains, followed by the ethyl acetate extracts The dichloromethane extracts had the anti-microbial potential in between ethyl acetate extracts and the water extracts The water extracts had little influence upon the growth of micro-organisms Among the plant parts, roots were more effective in inhibiting the growth of micro-organisms followed by flower extracts The stem extracts have a little effect upon the growth of micro-organisms	51
8	n-hexane soluble compounds	Aerial parts collected during different vegetative stages	Staphylococcus aureus, Listeria monocytogenes, Enterococcus faecalis, Escherichia coli, Bacillus subtilis, Proteus vulgaris, Salmonella sp., Candida albicans, Aspergillus niger and Fusarium moniliforme.	The unipolar fraction had insignificant anti-microbial activity against Staphylococcus aureus, Listeria monocytogenes, Enterococcus faecalis, and Escherichia coli The test microorganisms Bacillus subtilis, Proteus vulgaris, Salmonella sp., as well as the yeast Candida albicans were not inhibited in these concentrations. The mycelial growth of the filamentous fungi Aspergillus niger and Fusarium moniliforme also remained unaffected.	14
9	Hexan extract	Leaves	Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, and Proteus mirabilis	The extract was highly active against Staphylococcus aureus and moderately active against Escherichia coli and Klebsiella pneumoniae	32
10	Ethanol extract	Leaves	Different oral pathogenic clinical isolates	Anti-bacterial activity against most of the oral microbes tested especially cariogenic microbes such as Enterococcus faecalis and Streptococcus salivarius	46

Moreover, due to increased global travel and rapid urbanization, epidemic outbreaks caused by emerging and re-emerging viruses represent a critical threat to public health, particularly when preventive vaccines and anti-viral therapies are unavailable. To date, however, many viruses remain without effective immunization and only a few anti-viral drugs are licensed for clinical use. The situation is further worsened by the potential development of drug-resistant mutants. Hence, there is an urgent requirement to identify novel anti-virals that are very efficient and cost-effective for the management and control of viral infections when vaccines and standard therapies are lacking. Herbal medicines and purified natural products present a rich resource for novel anti-viral drug development[52]. The anti-viral activity of different dandelion extracts was tested against four viruses (Table 3).

ANTI-DEPRESSANT ACTIVITY

Depression is increasingly becoming a global public health problem and can result in many serious outcomes. Although progress had been made in the development of anti-depressants during the past several decades, the therapeutic efficacy is still unsatisfactory because of the numerous accompanying side effects. Hence, the task of discovering and developing safe and effective drugs for depression is important and urgent at present. Growing evidence indicates that natural products and natural product-derived compounds exhibited a remarkable anti-depressant-like effect. The anti-depressant-like effects of the water extract of dandelion leaves and roots were investigated in mice using forced swimming test (FST), tail suspension test (TST), and open field test (OFT). Chronic treatment decreased the immobility time in both FST and TST. Acute treatment also decreased the immobility time in both FST and TST. However, all treatments did not affect the locomotor activity in the OFT. Moreover, FST induced a significant increase in serum corticotropin-releasing hormone, adrenocorticotropic hormone, and corticosterone levels. Chronic treatment decreased serum corticotrophin releasing factor and corticosterone levels. These results demonstrated the anti-depressant effects of herb in animal models of behavioral despair and suggested the mechanism involved in the neuroendocrine system[57,58].

TABLE 3. *In vitro* anti-viral activity of dandelion extracts.

No.	Active constituents/ preparations	Parts of plant	Viruses	Results	Refs.
1	Aqueous extract	Whole plant	Human immunodeficiency virus 1	The level of replication and reverse transcriptase activity were decreased in a dose-dependent manner	53
2	Aqueous extract	Not mentioned	Influenza virus type A, human A/PR/8/34 and WSN (H1N1)	The extract inhibited infections in Madin-Darby canine kidney (MDCK) cells or Human lung adenocarcinoma cell line (A549) of PR8 or WSN viruses It inhibited polymerase activity and reduced virus nucleoprotein (NP) RNA level Mechanisms of reduction of viral growth in MDCK or A549 cells by dandelion involve inhibition on virus replication	54
3	Methanol extract	Leaves	Hepatitis C virus NS5B polymerase and whole virus as well in hepatoma cells	65% inhibition of NS5B expression was doc umented at nontoxic dose concentration 57% inhibition of virus replication was recorded when incubating Huh-7 cells with high titer serum of virus infected patients along with leaves extract Phytochemicals for instance D-glucopyranoside, Quercetin, Luteolin and some others displayed least binding energies as compared to standard drug Sofosbuvir The extract potentially blocked the viral replication and NS5B gene expression without posing any toxic effect on normal fibroblast cells	55
4	Water and methanol extracts	Leaves	Dengue virus serotype 2 (DENV2)	The high inhibitory effects of both extract on virus replication	56

Study about the anti-depressant effects of the methanol extract of dandelion and the underlying mechanism revealed that the extract at the dosage of 50 and 100 mg/kg alleviated the TST-induced immobility, and the effects were comparable to the anti-depressant drug Bupropion, which was used as the positive control. Dandelion extract exerts its effects by decreasing the levels of corticosterone and increasing the concentrations of dopamine, noradrenaline, and adrenaline. Moreover, the extract also increased the expression of brain-derived neurotrophic factor, which was associated with a decrease in the expression of mitogen-activated protein kinase phosphatase-1, indicative of the anti-depressant potential of dandelion. Finally, the active constituents of the extract, which include isoetin, hesperidin, naringenin, Kaempferol, sinapinic, and gallic acid, were also identified, which could potentially be responsible for its anti-depressant effects[59].

EFFECT ON FATIGUE

Fatigue is a common sign that may occur in both sickness and health. It can be divided into physical and mental fatigue. In China, Traditional Chinese Medicine has a long history of use as 'tonics' to treat physical fatigue and are now being validated by the scientific approach for their remarkable healing potential. Dandelion possessed an anti-physical fatigue effect. It enhanced the maximum swimming capacity of mice, dramatically delayed the lowering of glucose in the blood, and prevented the increase in lactate and triglyceride concentrations[60]. The anti-fatigue effect of dandelion in mice was tested by performing a FST and *in vitro* by using peritoneal macrophages. After daily oral administration of dandelion, blood biochemical parameters related to fatigue were measured after the FST. FST immobility time was decreased in the dandelion-treated group. Dandelion treatment increased glucose levels, serving as an energy source. The level of lactic dehydrogenase, which is an accurate indicator of muscle damage, tended to decrease after administration. When dandelion was orally administered to mice, blood urea nitrogen levels decreased[61].

ANTI-OXIDANT ACTIVITY

Aerobic mammals utilize oxygen to maintain normal physiological functions, and up to 2% of oxygen consumption ends in the form of reactive oxygen species (ROS). ROS are oxygen derivatives with unpaired orbital electrons and unstable and highly reactive. ROS includes hydroxyl radical, superoxide radical, peroxyl radical, and singlet oxygen. In addition to ROS, reactive nitrogen species such as nitric oxide (NO) and peroxynitrite, also have high reactivity with potentially important biological significance. Natural plant extracts have been investigated extensively for their anti-oxidant potential. The most common anti-oxidant compounds in fruits are ascorbic acid, carotenoids, and polyphenol substances. The quality of natural anti-oxidant depends not only on the nature of the plant source, geographical origin, weather conditions, time of harvesting and storage, but also on the method of extraction and the used solvent[1]. The anti-oxidant potential of different extracts of dandelion in diverse geographical areas has been listed in Supplementary Table 2.

ANTI-CANCER ACTIVITY

Cancer is the second cause of death worldwide. Numerous studies have suggested that consumption of a plant-based diet has a beneficial effect on cancer therapy. Over 60% of licensed and currently used chemotherapy drugs have been isolated from natural products, mostly of plant origin[82]. In 1981, for the first time, it was shown that the hot water extract of dandelion possessed anti-tumor activity[83]. After that several studies were conducted to approve the anti-cancer properties of dandelion and find the mechanism behind its effect on the adult and pediatric malignant cells (Supplementary Table 3). Dandelion shows a cancer cell-specific cytotoxicity[84]. It induces apoptotic cell death by raising the production of tumor necrosis factor (TNF)-α and interleukin (IL)-1α. Cytokines and their corresponding receptors are known to be important regulators of cell death. The TNF-α and IL-1α are two potent inducers of cancer cell apoptosis[85]. Dandelion induces apoptosis through both extrinsic (cell death receptor) and intrinsic (mitochondrial) pathways[84]. Besides its cytotoxic effect, it also reduces the invasion of cancer cells by lowering the phosphorylation levels of focal adhesion kinase and src as well as dampening the activities of matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9[86].

It was shown that dandelion down regulated the SRY-Box Transcription Factor 2 (Sox2) expression and increased the retinoic acid receptor ß2 (RARß2) gene and protein expression in cancer stem cells (CSCs)[87,88]. CSCs play a significant role in the initiation and progress of tumorigenesis. The conventional cancer therapies have incomplete and temporary effects that only shrink the tumor, and the tumor tends to relapse

mainly due to the multiple resistant mechanisms existing in CSCs. Sox2, one of the genes that maintains the self-renewal of embryonic stem cells and relates to the differentiation potential of these cells, is abnormally expressed in various human tumors. Sox2 plays an important role in tumorigenesis because over expression of Sox2 increases proliferation, clonogenicity, and tumorigenicity in cancer, and these results suggest that Sox2 is a potential therapeutic target molecule in cancer. RARß2, a member of the thyroid-steroid hormone receptor superfamily of nuclear transcriptional regulators, encodes RARß. It binds retinoic acid, the biologically active form of vitamin A which mediates cellular signaling in embryonic morphogenesis, cell growth, and differentiation. It is thought that this protein limits growth of many cell types by regulating gene expression. Tumor suppressor gene RARß2 expression is reduced in many malignancies (87). As mentioned before dandelion down regulates Sox2 expression and increased the RARß2 gene and protein expression in CSCs, so control apoptosis in cancer.

TNF-related apoptosis inducing-ligand (TRAIL) is a promising anti-cancer drug target that selectively induces apoptosis in cancer cells. However, many cancer cells are resistant to TRAIL-induced apoptosis. Hence, reversing TRAIL resistance is an important step for the development of effective TRAIL-based anti-cancer therapies. Knockdown of the TOR signaling pathway regulator-like (TIPRL) protein caused TRAIL-induced apoptosis by activation of the MKK7-c-Jun N-terminal Kinase (JNK) pathway through disruption of the MKK7-TIPRL interaction. Dandelion is a TRAIL sensitizer. Combination treatment with TRAIL targeting and dandelion resulted in TRAIL-induced apoptosis mediated through inhibition of the MKK7-TIPRL interaction and subsequent activation of MKK7-JNK phosphorylation. Chicoric acid as a major element of the dandelion extract, and combination treatment with chicoric acid and TRAIL induced TRAIL-induced cell apoptosis via JNK activation due to inhibition of the MKK7-TIPRL interaction[89].

DIFFERENTIATION-INDUCING ACTIVITY

Differentiation inducers are a new type of anti-cancer agent. Cell differentiation is necessary for normal growth and homeostasis, and drug-induced differentiation of tumor cells into benign or normal cells is an important approach for anti-cancer chemotherapy[98]. Lupeol, a lupane-type triterpene, in dandelion extract has differentiation-inducing activity. The differentiation-inducing effects of dandelion on the human leukemia cell line (HL60) and a B16 mouse melanoma-derived sub-clone with high differentiation capability (B16 2F2) were investigated. The extracts of dandelion root inhibited cell growth and induced melanogenesis of B16 2F2 cells. Chemical and physical data for the active compound were identical to those for lupeol[99].

GENO-PROTECTIVE ACTIVITY

Since the 1980s, an expanding body of experiments has confirmed that various plants could exert a substantial protective effect against human carcinogenesis by exerting anti-mutagenic properties and has suggested that natural products could be used as efficient chemopreventive agents against the genotoxic potential of xenobiotics, especially environmental carcinogens. Mitomycin C is currently applied to manage gastrointestinal and gynecological malignancies. It is a potent DNA cross-linker that induces DNA damage. Due to its powerful ability to generate deletion mutations and chromosome abnormalities, it is also considered as a common positive control for both *in vitro* and *in vivo* geno-toxicity/mutagenicity testing strategies. A study assessed the anti-mutagenic/anti-clastogenic activity of DIG (a liquid herbal preparation produced from a mixture of diluted mother tinctures of *Berberis vulgaris*, *Taraxacum officinale*, and *Arctium lappa*) toward the powerful genotoxic potential of mitomycin C using *in vitro* (micronucleus assay on Chinese hamster ovary cells (CHO)-K1) and *in vivo* (micronucleus and comet assays in mice) tests. DIG exerted a powerful anti-clastogenic activity, under both pretreatment and simultaneous treatment conditions as assessed by the micronucleus assay in CHO-K1 cells. Its protective activity was greater than that observed for each mother tincture. DIG decreased micronuclei levels in mouse erythrocytes and suppressed 80 % of DNA strand breaks in the liver, kidney, lung, brain, and testicles of mice exposed to mitomycin C[100].

DIURETIC AND KIDNEY-PROTECTIVE ACTIVITY

One class of clinical medicines used to lower blood pressure is known as diuretics and work by raising the excretion of urine from the body as well as the amount of sodium in the urine. There are an increasing number of studies indicating the

diuretic effects of herbal medicines[101]. The root of dandelion is a registered drug in Canada, sold principally as a diuretic[49]. Also, the German Standard License for dandelion tea includes stimulation of diuresis, and the German Commission E approves the use of dandelion for diuresis[102].

In 1979 the diuretic activity of dandelion was first quantified in a murine model reporting that the 4% aqueous extractive solution had a diuretic index superior to that found previously in other vegetal remedies, and it is comparable to that obtained with Furosemidum (a medication utilized to manage fluid build-up due to heart failure, liver scarring, or kidney disease), used as reference substance. The saluretic effect is also stronger than that recorded in various vegetal drugs. Also, the Leaves of dandelion were better diuretic and saluretic than the roots. Dandelion contains three times the amount of potassium in other botanical diuretics and provides more potassium than that lost from diuresis induced by ingesting dandelion[103]. Considering the requirement for potassium supplementation that typically accompanies the use of a pharmaceutical diuretic, dandelion could offer a therapeutically significant potassium contribution by replacing the potassium loss induced by most diuretics[102]. Opposite to this result, different study in 1993 showed that extracts and purified fractions isolated from autumn-collected dandelion roots had no significant effect on urine volume and sodium excretion in mice[104]. In a pilot study, a high-quality fresh ethanol extract of dandelion Leaves was ingested by volunteers to investigate the urinary frequency and volume. For the entire population, there was a significant increase in the frequency of urination in the 5 hours after the first administration. There was also a significant increase in the excretion ratio in the 5 hours after the second administration of the extract. The third administration failed to change any of the measured parameters. Based on these first human data, dandelion ethanol extract is promising as a diuretic agent[102].

Chronic kidney disorder has become a major cause of disability and in the worst situations leads to death. Major renal disorders happen due to diabetes and its complications termed as diabetic nephropathy. Also, nephrolithiasis occurs due to the presence of organic debris of carbohydrates, lipids, proteins and supersaturation with calcium oxalate in the renal system. Several herbs have proven to be used in the management of these disorders[105].

In a study, the protective effects of dandelion on the kidney are examined in female Wistar albino rats. The CCl4 was applied for kidney damage. Results revealed that dandelion extract which was used against histopathological changes in the kidney caused by toxication presented a curative effect, which was supported by biochemical parameters[106].

In a similar study revealed that this protective effect is possible by increasing the anti-oxidant defense system by dandelion extract[107]. So, regular intake of dandelion along with conventional medicine can be beneficial in treating kidney injury and would improve the working efficiency of the kidney while preventing any damage and side effects.

PROTECTIVE EFFECT ON LUNG INJURY

Acute lung injury (ALI) is described as a syndrome of lung inflammation with increased vascular permeability. The principal features of ALI are extensive neutrophil influx into the lungs, the production of pro-inflammatory mediators from inflammatory cells, and damage to lung epithelial and endothelial surfaces leading to protein-rich edema and impairment of respiratory function. Although recent progresses in clinical management and extensive researches into new strategies for treatment have shown promise, the mortality from it remains high in the last decade. The development of efficient therapeutic approaches is urgently needed. The *in vivo* study about the protective effect of dandelion on ALI induced by lipopolysaccharide (LPS) in mice showed that dandelion decreased the lung wet-to-dry ratio, protein concentration and the number of neutrophils in the bronchoalveolar lavage fluid after LPS challenge. It decreased LPS induced myeloperoxidase activity and increased superoxide dismutases activity in the lungs. Besides, histopathological examination indicated that dandelion attenuated tissue injury of the lungs in LPS-induced ALI. Besides, dandelion inhibited the production of inflammatory cytokines TNF-α and IL-6 in the bronchoalveolar lavage fluid LPS challenge in a dose-dependent manner. These results suggested that dandelion protects against LPS-induced ALI in mice[108].

PANCREAS-PROTECTIVE ACTIVITY

Cholecystokinin (CCK), a gut-brain peptide, was initially identified as a gastrointestinal hormone, and subsequently found in the central and peripheral nervous system and cholecystokinin octapeptide (CCK-8) is the predominant form in the central nervous system (CNS) and acts as an anti-opioid peptide under certain circumstances. CCK-8 is known to exert trophic effects on the pancreas in several species. But high doses of CCK octapep-

tide fail to promote pancreatic tropism; furthermore, they can induce oedematous pancreatitis. Cells could respond to heat shock or other stresses by the rapid synthesis of heat shock proteins (HSPs). The induction of heat shock responses enhances the ability of the cells to overcome the effects of stresses. It was stated that the pre-induction of HSP expression had a protective effect against cerulein-induced pancreatitis in rats or choline-deficient ethionine-supplemented diet model pancreatitis in mice. With increasing neutrophil migration to the pancreas, a variety of inflammatory cytokines are released. These include IL-1, IL-6, IL-8, platelet activating factor, and TNF. The effect of dandelion on CCK-8-induced acute pancreatitis in rats was tested. Repeated CCK-8 treatment resulted in the typical laboratory and morphological changes of experimentally-induced pancreatitis. Dandelion decreased the pancreatic weight/body weight ratio in CCK-8-induced acute pancreatitis. It also increased the pancreatic levels of HSP60 and HSP72. Additionally, the secretion of IL-6 and TNF-α decreased in the animals treated[109].

HEPATO-PROTECTIVE ACTIVITY

The healthy state of the body depends on the precise functioning of the liver for excretion of wastes, xenobiotic metabolism and its dysfunction by toxic chemicals results in serious health problem. Hepatic malfunction due to inhalation or ingestion of hepatotoxic materials such as acetaminophen, cadmium chloride, ethanol, carbon tetrachloride (CCl4), and allyalcohols are significantly increasing worldwide. Plants used in traditional medicine need a detailed investigation from an ethnopharmacological approach for the treatment of liver disorders[110]. The hepato-protective effect of dandelion was tested in some studies (Supplementary Table 4).

NEURO-PROTECTIVE ACTIVITY

The CNS, with a high polyunsaturated fatty acid content, high oxygen consumption, and weak anti-oxidative systems, is particularly vulnerable to oxidative stress (OS), which causes neuro-de-

TABLE 4. Anti-diabetic activity of dandelion extracts.

No.	Active constituents/ preparations	Parts of plant	Study design	Results	Refs.
1	Dandelion	Whole plant	*In vivo* (Male, powder in water adult, healthy albino rabbits)	The powders of plant produced hypoglycaemic effects in normal but not in Alloxan-treated animals Acute toxicity and behavioral changes were not observed Plant contains some hypoglycaemic principles which act probably by initiating the release of insulin from pancreatic beta-cells of normal animals	123
2	Water extracts	Leaves	In vivo (Male Sprague-Dawley rats)	The extract did not affect the serum glucose concentration in normal rats It improved the hyperglycemia induced by streptozotocin	124
3	Water extract	Whole plant	*In vitro* (Enzyme assay)	Dandelion showed α-glucosidase inhibitory activity	126
4	Dandelion herb	Whole plant	Case report (a 58 year-old-woman with a known history of type 2 diabetes mellitus)	The hypoglycemia effect due to the ingestion of dandelion	129
5	Methanol and water extracts	Roots, flowers and stems	*In vitro* (Enzyme assay)	Inhibitory activity against α-amylase enzyme The water extracts of all the plant parts showed marginally more inhibitory effect as compared to the methanol extracts which could be due the more ionic constituents in the water extracts than in the methanol extracts Among the all parts of the plant the stem showed the highest overall inhibitory effect of both α-amylase and α-glucosidase Dandelion had more profound effect upon α-amylase enzyme than on the α-glucosidase enzyme	130

generative diseases. Understood from *in vitro* and *in vivo* investigations, heme oxygenase (HO) is a dynamic sensor of cellular OS and likely arbiters of tissue redox homeostasis. HO-1 is exquisitely sensitive to induction by OS compared to other HO proteins. Past reports have indicated that HO-1 has neuro-protective action. Induction of HO-1 expression can be used to protect brain cells against oxidative and neuro-degenerative conditions. The neuro-protective effects of ethanol extracts of dandelion on glutamate-induced OS in HT22 cells were tested. Both cell viability and ROS assays confirmed that extract effectively attenuated glutamate-induced cytotoxicity and ROS generation. Moreover, extract increased the expression of HO-1 and promoted the nuclear translocation of nuclear factor erythroid 2-related factor-2 (Nrf2). The inhibitory effects of the extract on glutamate-stimulated cell toxicity and ROS production were partially reversed by tin protoporphyrin (SnPP), a HO activity inhibitor. Taken together, this extract can protect HT22 cells against glutamate-induced oxidative damage by inducing the Nrf2/HO-1 pathways[119]. In another study, just the extract of the aerial parts showed cyto-protective effects on glutamate-induced neurotoxicity and induced the expression of HO-1 in the mouse hippocampal HT22 cells, while the roots extract did not show neuro-protective effect. So, the extract of the aerial parts could be an effective candidate for the treatment of ROS related neurological diseases[120].

The toxic effects of prenatal exposure to lead acetate on brain tissues of newborn rats and potent protective effects of dandelion added to rat diet were tested in female rats. Lead acetate was administered to one-half of these rats through drinking water. Lead poisoning of mothers caused lead deposition in the brain and cerebellum of newborns and cerebellum tissue damages. Furthermore, a significant decrease in weight and protein content of these tissues was found. OS and changes in anti-oxidant enzymes activity in brain tissues were also recorded. Conversely, no such damages or biochemical changes were found in neonates from plant fed Pb-poisoned mothers. These results strongly suggest that beneficial effects of the dandelion-added diet on lead-intoxicated rats proceeded through the reduction of the Pb-induced OS and related damages[121].

ANTI-DIABETIC ACTIVITY

Diabetes mellitus is one of the most serious health problems worldwide. It is a chronic disease resulting in persistent hyperglycemia due to imbalanced glucose metabolism. Although there are several therapy approaches, it is challenging to achieve optimal glycemic control without adverse effects. Therefore, research is continuing to find novel anti-diabetic agents. Plants and herbs have been utilized for centuries as a natural remedy for diabetes[122]. For the first time in 1985, it was shown that dandelion had significant hypoglycaemic effects[123]. From that time numerous studies examined the anti-diabetic activity of different parts of dandelion (Table 4).

Dandelion also reduces diabetic complications. Study about alternation of hepatic anti-oxidant enzymes activity and lipid profile in streptozotocin-induced diabetic rats by supplementation of dandelion water extract revealed that when dandelion was given to the diabetic rats, the anti-oxidant enzymes activity returned to near-control values. However, there was no difference in the mRNA expression concentrations of these enzymes. It also lowered the hepatic malondialdehyde concentration in the diabetic-induced rats. So, dandelion can improve lipid metabolism and is advantageous in preventing diabetic complications from lipid peroxidation and free radicals in diabetic rats[124].

α-Glucosidase (α-d-glucoside glucohydrolase) (EC 3.2.1.20) is an enzyme that catalyzes the liberation of α-glucose from the no reducing end of the substrate. It is a membrane-bound enzyme in the epithelium of the small intestine, which works to promote the absorption of glucose by the small intestine by catalyzing the hydrolytic cleavage of oligosaccharides into absorbable monosaccharides. By the inhibition of α-glucosidase in the intestine, the rate of hydrolytic cleavage of oligosaccharide is decreased and the process of carbohydrate digestion spreads to the lower part of the small intestine. This spreading of the digestion process delays the overall absorption rate of glucose into the blood. This has proved to be one of the best strategies to reduce the postprandial increase in blood glucose and in turn help avoiding the onset of late diabetic complications. There are some reports of the presence of α-glucosidase inhibitors, such as nojirimycin and 1-deoxynojirimycin in plants. α-Glucosidase inhibitory potency of plant extracts and isolated compounds from various origins are discussed extensively in a review by Kumar et al[125]. The anti-diabetic effect of dandelion is in part due to the α-glucosidase inhibitory activity[126] (Figure 2). This inhibition is a mixed-type as observed from their Lineweaver-Burk plots[127].

A review systematically identified and gathered the scientific data available on the anti-diabetic effect of dandelion roots and Leaves in

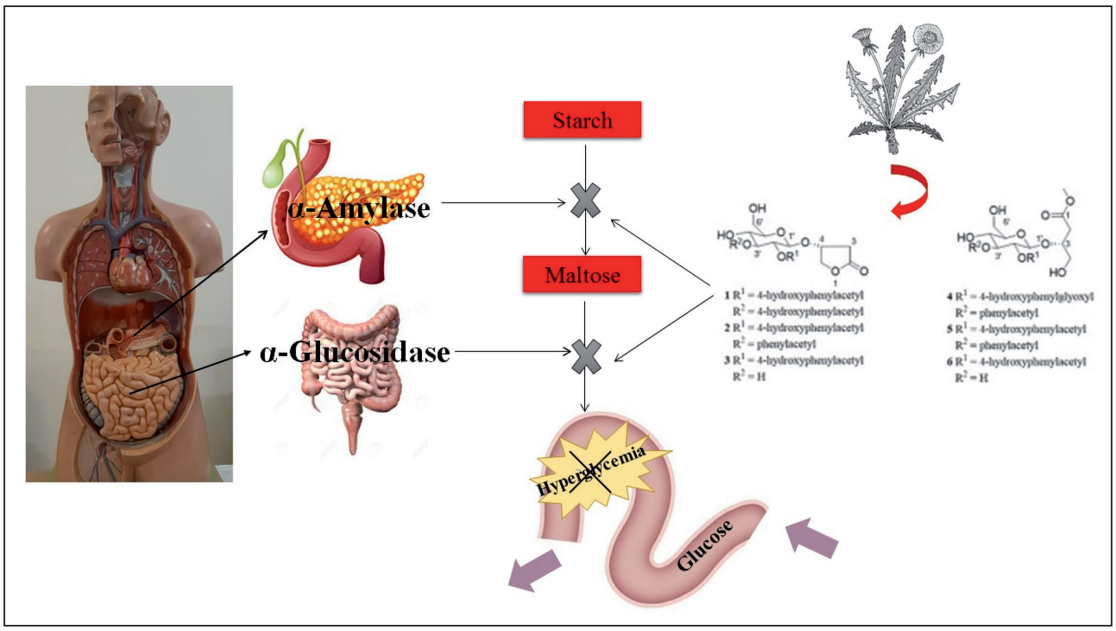

Fig. 2. Anti-diabetic activity of dandelion.

patients with type 2 diabetes. This study claimed that a big gap exists in the use of dandelion as an anti-diabetic herb, although numerous studies have demonstrated its therapeutic uses. So, there is a need for well-designed clinical trials in this subject[128].

EFFECT ON STOMACH MOTILITY

Disorders of stomach motility are involved in gastroenterological diseases. Prokinetic agents such as domperidone and cisapride are important therapeutic remedies, but these biochemically synthesized drugs have some side effects. Natural products are important for the prevention and treatment of gastrointestinal disorders. Dandelion has long been used for the treatment of abdominal distension, dyspepsia, nausea, and vomiting. Dandelion roots and leaves are used widely in Europe for gastrointestinal ailments. The German Commission E and European Scientific Cooperative for Phytotherapy recommend dandelion root to treat stomach upset, dyspepsia, and loss of appetite. Also, it has been shown that dandelion causes notable contraction of colonic smooth muscle cells in rats. Overall, some evidence suggests that dandelion may have some effects on gastrointestinal smooth muscle motility. Gastric emptying (GE) is related to smooth muscle contraction. Ethyl acetate fraction, n-butanol fraction, and aqueous fraction were prepared in succession from 70% ethanol extract of dandelion using solvent polarity chromatography. Phenol red meal was adopted to estimate GE in mice. n-butanol fraction was determined to be most effective in accelerating GE. This stimulatory effect of n-butanol fraction on GE was also supported by the observation that n-butanol fraction increased spontaneous contraction of gastric fundus and antrum and reduced the spontaneous motility of pyloric sphincter *in vitro*. Atropine blocked the stimulatory effect of n-butanol fraction on GE, whereas phentolamine and propranolol did not affect[131].

IMMUNOSTIMULATORY ACTIVITY

An aqueous extract of dandelion restored the inhibition of NO production by mouse peritoneal macrophages pretreated with cadmium in a dose-dependent manner. This effect was mainly dependent on dandelion-induced TNF-α secretion. So the potential of dandelion to restore NO production from interferon-γ (IFN-γ)-primed mouse peritoneal macrophages is the result of dandelion-induced TNF-α secretion[132]. Stimulation of mouse peritoneal macrophages with dandelion after the treatment with recombinant interferon-γ (rIFN-γ) resulted in increased NO synthesis. Dandelion did not affect NO synthesis by itself. When dandelion was applied in combination with rIFN-γ, there was a marked cooperative induction of NO synthesis in a dose-dependent manner. The optimal effect of dandelion on NO synthesis was shown 6 hr after treatment with rIFN-γ. This increase in NO syn-

thesis was manifested as an increased amount of inducible NO synthase protein. NO production was repressed by NG-monomethyl-L-arginine. The increased production of NO from rIFN-γ plus dandelion-stimulated cells was decreased by treatment with a protein kinase C inhibitor such as staurosporin. Besides, the synergy between rIFN-γ and dandelion was mainly dependent on dandelion-induced TNF-α secretion. Considering the potent impact of endotoxin on TNF-α production, all the preparations of dandelion were endotoxin-free. These results suggested that the capacity of dandelion to increase NO production from rIFN-γ-primed mouse peritoneal macrophages is the result of dandelion-induced TNF-α secretion[133]. Prolonged use of chemotherapy can weaken the immune system. For instance, although the doxorubicin is an effective chemotherapeutic drug, it has considerable side effects such as cardio-toxicity, susceptibility to infectious disease, hair loss, and sore throat. Besides, doxorubicin affects the immune system by reducing the expression of IL1-α, IFN-γ production, natural killer cells, lymphocyte proliferation, and the ratio of CD4 + / CD8 +. Since, an agent that works synergy with doxorubicin, but can reduce its immunosuppressive side effects appears necessary. Now, there are various materials which otherwise could increase the body's resistance to a disease called as immunostimulants. Ethanol extract of dandelion leaves was able to increase the secretion of TNF-α and IL-1. TNF-α works together with IL-1 as the functional non-specific anti-tumor immunity. Dandelion leaves can influence the anti-inflammatory response through the inhibition of synthesis of NO and inhibition of COX-2 expression. Accordingly, they can be considered as immunostimulatory for combination with doxorubicin (co-chemotherapy). A study determined the effect of ethanol extract of dandelion in the immune system of Sprague Dawley rat that induced by doxorubicin to observe the profile of immune cells. Doxorubicin combined with extract increased the number of leukocytes, lymphocytes, neutrophils, cytotoxic CD8 + T cells compared to the control doxorubicin alone group. Data showed that ethanol extract of leaves possessed immunostimulatory activity and potential as co-chemotherapy agents[134]. *In vitro* tests in mouse peritoneal macrophages revealed that TNF-α production and mRNA expression were increased by dandelion in combination with rIFN-γ treatment in macrophages. Besides, IL-12 p70 production and mRNA expression were increased with dandelion in combination with rIFN-γ. To determine the effect of dandelion on the production of TNF-α in mouse peritoneal macrophages, both non-primed (resting) and rIFN-γ-primed cells were treated. rIFN-γ-induced TNF-α production in the group treated with dandelion. Dandelion in combination with rIFN-γ or dandelion alone increased the production of IL-12p70. Treatment with dandelion was found to significantly increase the mRNA levels of TNF-α and IL-12p70, whereas it did not affect the expression of the housekeeping β-actin gene[61]. Hot-water (100 ˚C) and cold-water (4 ˚C) extracts of dandelion root were assessed for the effects of innate and adaptive immune responses in mice. Both extracts did not affect the viability of macrophages at low concentrations. The thioglycollate-induced macrophages treated with extracts produced a significantly higher quantity of various cytokines, such as IL-6 and IL-12 than those treated with the medium. So, the extracts potently stimulated the innate immune response. When mice were subcutaneously immunized with ovalbumin plus Freund's incomplete adjuvant-emulsified hot water extract, the extract did not affect the production of IgE but enhanced the production of IgG1, IgG2a, and IgG2b. The culture supernatant obtained from the splenocytes of mice treated with ovalbumin plus Freund's incomplete adjuvant-emulsified hot water extract also evidenced raised levels of both ovalbumin-specific Th1-type (IFN-γ) and Th2-type cytokines (IL-4, IL-6 and IL-10). So, it seems that hot water extract can modulate the immune responses to allergens in mice[135].

ANTI-INFLAMMATORY ACTIVITY

Inflammation is a complex pathophysiological process mediated by a variety of signaling molecules generated by leukocytes, macrophages, and mast cells. Inflammation is a tissue response to injury characterized by enhanced blood flow to the tissue causing raised temperature, redness, swelling, and pain. Macrophages perform an important role in the inflammatory condition through the release of inflammatory mediators such as NO, prostaglandin (PG) E2, and pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. There are some studies about the anti-inflammatory effect of dandelion (Supplementary Table 5). The mechanism of action for dandelion anti-inflammatory activity may be through the reduction in NO production (via NO synthesis inhibition), COX-2 expression, and PGE2 by luteolin and luteolin-7-O-glucoside[136-137].

BIFIDOGENIC EFFECT

Bifidobacteria constitute a major part of the human intestinal microflora and have proved considerable health-promoting benefits to the host. It was reported that the infusion of dandelion root stim-

ulated the growth of 14 strains of bifidobacteria *in vitro*. The utilization of oligofructans, glucose, fructose, and total saccharides was determined by enzymatic and phenol-sulfuric methods. Dandelion oligofructans were an important source of carbon and energy for bifidobacteria tested[146].

EFFECT ON HEMATOLOGICAL PROFILE

A study about the effect of hydro-alcoholic extract of dandelion on blood cells in mice showed that the number of red blood cells (RBCs), white blood cells (WBCs), lymphocyte, and the rate of hemoglobin (Hb) were increased. The rate of platelet was decreased. So, the study indicated the efficacy of dandelion extract on RBC and HB and on WBC to achieve normal body balance[156]. Also, the effect of aqueous extract of dandelion leaves on the hematological indices of rats poisoned with CCl4 showed an elevation in the levels of WBC and bilirubin and a decrease in packed cell volume (PCV) and Hb occasioned by CCl4 relative to control samples. The increase in the WBC is attributed to stimulation of the immune system response caused by the toxicity of CCl4; there was also an indication of anemia and hemolysis in the blood of the experimental rats. After three weeks of oral administration of 100 mL and 200 mL aqueous extract, there was a decrease in WBC and bilirubin levels, with a corresponding increase on PCV and Hb. It was also observed that the functional recovery of these blood indices was concentration-dependent[147].

EFFECT ON DYSLIPIDEMIA

Empirically, dandelion (especially its root) is used against obesity. In 1974 it was shown that the fluid extract of dandelion given in a dose of 8 ml/kg body weight for a month caused a loss weight in mice and rats about as much as 30% in comparison with the initial values[103]. Global strategies based on lifestyle modifications and weight loss medicines have failed to provide lasting weight loss in overweight people. According to the WHO, obesity has become a worldwide epidemic. It is a major public health problem and usually followed by metabolic disorders, diabetes, hypertension, cancer, cardiovascular diseases, and inflammation-related diseases[148]. Various studies have evaluated natural products with anti-obesity activity, including plant materials. Some studies also have examined the dandelion effect on hyperlipidemia-related conditions (Supplementary Table 6).

EFFECT ON INTRACELLULAR SIGNALING CASCADES

Study about the effects of an ethanol dandelion root extract on Ca2+ signaling in the human embryonic kidney (HEK) 293 cells showed that extract (10-400 µg/mL) exposure, in the presence of external Ca2+, dose-dependently raised intracellular Ca2+ levels. The extract-induced Ca2+ increase was decreased in the absence of extracellular Ca2+. In addition, extract caused Ca2+ release from the endoplasmic reticulum of intact cells. This extract directly activates both the release of Ca2+ from internal stores and a significant Ca2+ influx at the plasma membrane. The resulting high Ca2+ levels within the cell directly stimulate phospholipase C activity[154].

STEROIDOGENIC EFFECT

For many years, some medicinal plants have been used to regulate steroidogenesis or late-onset hypogonadism. Steroidogenic enzymes are involved in the production of testosterone in the testis. A study about the steroidogenic effect of dandelion extract on mouse TM3 Leydig cells, which produce male hormones by increasing the levels of steroidogenic enzymes showed that dandelion increased the mRNA and protein levels of steroidogenic enzymes, thereby increasing the testosterone levels in mouse Leydig cells[155].

CONCLUSIONS

An increase in the popularity of alternative medicine and natural products has renewed interest in plant compounds and their derivatives as potential natural medicines. Although the results from this review are completely promising for the use of dandelion as a medicinal agent, however, three limitations currently exist in the published literature. 1) Some clinical trials should be conducted to support its beneficial use; 2) long-term trials with reasonable duration would provide insights into the possible side-effects of different extract of this plant; 3) the detailed mechanisms of action underlying the therapeutic potentials of dandelion should be understood.

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Author's contributions:
M. Taghadosi and I. Rashidi designed the study and co-authored the manuscript. F. Bahrehmand and S. S. Miraghaee performed the entire search. M. Pazhouhi and c. Jalili wrote the manuscript. M. Sohrabi edited the manuscipt. All authors read and approved the final manuscript.

Conflict of interest:
The authors declare that they have no conflict of interest.

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