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Dandelion: Phytochemistry and clinical potential

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Abstract
Taraxacumofficinale (dandelion), a member of the Asteraceae family, commonly found in the temperate zone of the Northern hemisphere, is a herb that grows to a height of about 12 inches, producing spatula-like leaves and yellow flowers that bloom year round. Dandelion is used in many traditional and modern herbal medical systems, as particularly has been documented in Asia, Europe, and North America. Dandelion is grown commercially in the United States and Europe, the leaves and roots are used in herbal medicine. It iscommonly used as a food. Sesquiterpene lactones impart a bitter taste to the plant, which is especially notable in the leaf but also in the root particularly when spring-harvested. Preclinical research on dandelion has revealed numerous properties, including its actions as an inflammation modulator, diuretic, digestive stimulant, insulin stimulant, demulcent, prebiotic, immunomodulator, antiangiogenic, and anti-neoplastic. Dandelion root and leaf could protect against oxidative stress linked atherosclerosis and decrease the atherogenic index. Dandelion offers a compelling profile of bioactive components with potential anti-diabetic properties. *Taraxacumofficinale* has been used in folk medicine in the treatment of hepatic and several diseases such as breast and uterus cancers. Dandelion extract has a potent inhibitory activity against HIV-1 replication and reverse transcriptase (RT) activity.Several flavonoids including caffeic acid, chlorogenic acid, luteolin, and luteolin 7-glucoside have been isolated from the dandelion. *Taraxacumofficinale* leaves are rich in fiber, potassium, iron, calcium, magnesium, phosphorus, vitamins A and C, the B vitamins thiamine and riboflavin, and protein. The aim of this review is to evaluate the properties of dandelion with exploration of its diverse biological activities.

Keywords: *Dandelion,* diuretic, oxidative stress, sesquiterpene, type 2 diabetes

Introduction
History of using herbs to treat diseases and health gain has been common in human societies.Large numbers of drugs are being isolated and extracted from herbs. The medicinal plants andherbs are the sources of secondary metabolites and essential oils of therapeutic importance. The important advantages against the therapeutic use of medicinal plants in various ailments and disorders are their safety besides being economical, effective and easily available. *Taraxacumofficinale*, commonly called Dandelion, is a herbaceous perennial belonging to family Asteraceae (Compositae) (Damylo *et al.*,1984) [8]. This herb usually has deeply toothed hairless leaves, 5–30cm long and 1–10cm wide. It grows 3–35cm in height, forming a rosette of leaves at ground level. It has single, golden yellow flowers on straight leafless hollow stems, which emerge from the centre of the rosette. Each flower consists of a collection of florets. Dandelion plants have tap roots, tapering from 2 to 3cm wide and at least 15cm in length. Roots are fleshy and brittle, and area dark brown color on the outside and white on the inside. It was native to Europe but now can be found throughout the northern temperate zones (Ali *et al.*, 1989) [2]. Dandelion is a rich source of vitamins and minerals and is particularly high in vitamins A and C and iron, carrying more iron and calcium than spinach (Ali *et al*., 1989) [2]. The concerned plant is being consumed in the Kashmir valley from times immoral as source of vegetable and for the lactating mothers as a source of minerals especially calcium. It is used for treatment of jaundice and disorders of the liver, gallbladder and other various hepatic ailments (You *et al*., 2010; Ahmed *et al*., 2013,) [36, 1]. The folk medicines of China, India, and Russia have recognized dandelion's effect as a liver tonic. Traditional Chinese medicine combines dandelion with other herbs to treat hepatitis (Modaresi, 2012) [22]. Conventionally, root and herb from *Taraxacumofficinale* (TO) has been reported to be used for the treatment of various ailments, including liver and gallbladder disorders. It is used to enhance the immune response to upper respiratory tract infections, bronchitis and pneumonia, and as a topical compress to treat mastitis, anemia and inflammation (Blumental *et al*. 2000) [18].

Wolbis *et al.,* 1993 [34] carried out an analysis in which he mentioned and isolated various polyphenolic compounds from *T. officinale* plant extracts thereby showing that the plant is rich in various antioxidants and can have a direct effect of these phytochemicals on health of an organism. Cinnamic acid, coumarins and flavonoids and other phytochemicals bearing important medicinal and therapeutic importance have been isolated from different tissue of *T. officinale* plant by various analytical methods by Williams *et al*.,1996 [33]. Budzianwski *et al*., 1997 [3] has isolated a large number of Coumarins and caffeyl tartaric acid from the leaves of *T. officinale.* Modern pharmacological research suggests this plant has broad-spectrum antibacterial (Woods-Panzaru *et al*., 2009) [35], anti-fungal (Odintsova *et al*., 2010) [23], antiviral, antidiabetic, choleretic, antirheumatic, anti-inflammatory (Koh *et al*., 2010) [12], hepatoprotective, diuretic, and tumor apoptosis-inducing properties (Schutz *et al.,* 2006) [30].

Virus cell-based fluorescence assay using pseudotype particles is an efficient and cost-effective screening system that has been used for primary screening of novel agents against HIV-1 (Lindsten *et al*., 2001) [17]. Pseudotyped viruses produced in this system can mimic most stages of the HIV- 1 life cycle, including viral protein production, assembly, release, maturation, entry, integration and replication without producing replication-competent viruses. This approach has the potential to identify inhibitors against multiple viral and cellular functions essential for HIV. The results suggested that *T. officinale* extract has a potent inhibitory activity against HIV-1 replication and RT activity.

Dandelion is a commonly available food with a long historyof human use and as such poses little risk of harm. Dandelionextracts are listed on the US Food and Drug Administration's"generally recognized as safe" (GRAS) list for foods and supplements (Vogel, 1977) [32].

Chemical Composition

Among the most important compounds in dandelion aresesquiterpene lactonesalso known as bitter elements principally taraxacin and taraxacerin (Leung *et al*., 1996) [15], (believed to have anti-inflammatory and anticancereffects).Other related compounds include beta-amyrin, taraxasterol, and taraxerol, as well as free sterols (sitosterin, stigmasterin, and phytosterin), phenylpropanoids (believed to have inflammationmodulatingeffects), triterpenoid saponins and polysaccharides(primarily fructosans and inulin), smaller amounts of pectin, resin (complexcarbohydrates). Three flavonoid glycosides – luteolin7-glucoside and two luteolin 7-diglucosides – have been isolated from its flowers and leaves. Hydroxycinnamic acids, chicoric acid, monocaffeyltartaric acid, and chlorogenic acid are found throughout the plant, and the coumarins, cichoriin, and aesculin have been identified in theleafextracts (Williams *et al*.,1996) [33]. Dandelion leaves are a rich source of a variety of vitamins and minerals, including beta carotene, non-provitamin A carotenoids, xanthophylls, chlorophyll, vitamins C and D, many of the B-complex vitamins, choline, iron, silicon, magnesium, sodium, potassium, zinc, manganese, copper, and phosphorous.

Pharmacology

Dandelion leaf and root have both been studied for theireffects on digestion, mostly as bitter digestive stimulants. Dandelionroot has been investigated for demulcent, prebiotic, hypoglycemic, and immune-modulating effects. Dandelion leaf has also beeninvestigated as a diuretic and inflammation modulator.

Demulcent and Prebiotic Activity

Dandelion roots have adistinct demulcent action andprebiotic properties due to their contentof inulin. Sesquiterpenelactones impart a bitter taste to the plant, which is especially notablein the leaf but also in the root (particularly when spring-harvested). These compounds also likely explain the increase in bile production seen in animal studies with dandelion, with the studiesthemselves lending support to the traditional use of dandelion as abitter digestive stimulant. One study showed that sesquiterpenelactones contributed to the inflammation-modulating properties ofdandelion root. Other studies showed that crude extracts of both root andflower modulated inflammation, and some evidence suggeststhat phenylpropanoids might be key to this activity. Ethanolextracts of the dried aerial parts have been shown in rodent studiesto reduce inflammation and inhibit angiogenesis, thoughwhich constituents were responsible for these effects were notinvestigated.

For most clinical uses, dandelion has not been scrutinized rigorously according to modernscientific methods. Traditionally, the leaf is regarded as a usefulbitter and moderately potent diuretic. The German Commission E approves the use of dandelionas a diuretic and also for use in anorexia, dyspepsia, and biliaryabnormalities (Ali *et al*., 1989) [2].

Gastrointestinal Complaints

The use of dandelion leaf forindigestion or other atonic gastrointestinal complaints is alsolargely unverified by modern studies. However, a case series of24 patients with nonspecific, chronic colitis treated with a formulaconsisting of dandelion (specifically, *T officinal*), St John'swort (*Hypericum perforatum*), lemon balm (*Melissa officinalis*), calendula (*Calendula officinalis*), and fennel (*Foeniculum vulgare*)demonstrated remarkable symptomatic improvement in termsof stool normalization and pain reduction (Racz-Kotilla *et al*.,1974) [26].

Anti-diabetic properties of dandelionand its components

The bioactive components in dandelion havedemonstrated a series of anti-diabetic effects, which are due to the pharmacological actions ofcomponents such as sesquiterpene lactones, triterpenes/phytosterols (taraxasterol), phenols, flavonoids,and phenolic acids (Schütz*et al*., 2006) [30]. The main factor in T2D is the dysregulation ofinsulin secretion and insulin sensitivity that leadsto increased blood sugar levels (hyperglycemia)and T2D, which can later cause the development ofvascular diseases (Resnick *et al*.,2002) [27]. As T2D is both an epidemicphenomenon and a huge economic and social burden,many countries are becoming more reliant onanti-diabetic medicines (Onal *et al*., 2005) [24]. The root of dandelioncontains inulin which includes fructooligosaccharides (FOS). FOS is a complex carbohydrate; its intake benefits bifido-bacteria, whicheliminate pathogens in the gastrointestinal tract. As a result of mineral absorption, FOS stimulatesthe immune system, and thereby suppressesab normal cell growth. This complex carbohydratecan help to normalize blood sugar levels. The plant extractsreduces hyperglycemiawhen used in high levels of water extract. Chlorogenic acid (CGA) has been a potential compound for preventingobesity and inflammation. It also impacts oninsulin secretion and sensitivity, making it an attractiveoption for use as a future

anti-diabeticdrug.

Action mechanisms of dandelion in Type -2 diabetes (T2D)

T2D impacts many biological systems that influencethe proper function of lipid metabolism, glucose metabolism, and insulin regulation. Glucoseis the main energy source for most organs ofthe body and insufficient release of insulin by theβ-cells to control glucose levels leads to metabolicdisorders. Therefore, a possible explanation for the effects and mechanisms of dandelion on T2D couldbe its interaction with factors involved in the metabolic syndrome (lipid metabolism, glucose metabolism, protein metabolism, α- and β-cells dysfunction) (Grundy *et al*., 2004) [10]. The mechanisms by which plant-derived compoundsmanifest their anti-diabetic properties are (Mir *et al*., 2015) [21]:

1. Inhibition of renal glucose reabsorption.
2. Reduction of the activity of carbohydrate enzymes (α-amylase with β-galactosidase andα-glucosidase).
3. Reduction of dietary blood sugar (whichstimulates hepatic glycolysis and glycogenesis).
4. Inhibition of potassium channel flow.

Anti-inflammatory action

Seo *et al*. (2005) [31] showed that dandelion leaf extracthas anti-inflammatory properties, which mayprotect against cholecystokinin-induced acute pancreatitisin rats. Cholecystokinin is known toexert trophic effects in several species.*Taraxacumofficinale* hasbeen used to cure liver and gallbladder disorders,which is attributable to its content of terpenoidand bitter sterol components such as taraxacinand taraxacerin. Koo *et al.* (2004) [31] found that *Taraxacumofficinale* induces apoptosis of human hepatoma (HepG2) cells through tumor necrosis factor α (TNF-α) andinterleukin (IL) 1α secretion, implying anti-inflammatory effects within the central nervoussystem.

Anti-oxidative properties

It has also been shown that glucose may generateROS in β-cells, implying that glucose-inducedoxidative stress is a mechanism of glucose toxicity (Robertson *et al.*, 2007) [28]. The process of ROS formation involves autooxidation,oxidative phosphorylation, glycosylation, and glucosamine pathways (Robertson *et al*., 2004) [29]. Excess RO Sproduction requires anti-oxidant defense, which isprovided by dandelion extract, as is known fromseveral studies conducted both *in vitro* and *in vivo* (You *et al*., 2010) [36]. Flowers from dandelion are potential antioxidantresources, exerting their effect by way oftheir rich content of phenolic components includingflavonoids, coumaric acid, and ascorbic acid. Their leaf extracts are effective hydrogen donors,hydrogen peroxide scavengers, and reducingagents. Several studies have demonstratedthe anti-oxidative effect of dandelion. According to Hagymasi *et al.* (2000) [11], extracts from dandelionleaf and root are hydrogen-donating, ROS formation-inhibiting, and radical-scavenging. In anotherrecent study of dandelion flower extracts, ethyl acetate fraction scavenged ROS by preventing DNA from ROS-induced damage. The prevention of oxidative stress was due to the presence of bioactive components including luteolin and luteolin7-O-glucoside.

Action of dandelion on digestion, glycolysis, and Krebs cycle

Mitochondria plays another critical role in theonset of insulin resistance as they are the site atwhich the Krebs cycle and fatty acid oxidation takeplace. Their dysfunction may cause the accumulationof fat in muscle tissue and subsequently thedecrease of adenosine triphosphate (ATP) in membranetransport. Bioactive components indandelion may be able to regulate these pathways,possibly via inhibition of certain enzymes that digestcarbohydrates (Prabhakar *et al*., 2008) [25]. The pathways involved are the glycolytic cycle and Krebs cycle, in additionto other pathways involved in the release of insulinfrom β-cells. Chlorogenic acid andchicory acid(CRA) may activate glucokinasein glycolysis, which catalyzes the phosphorylationof glucose to glucose-6-phosphate(G6P) (Coman *et al.*,2012) [7]. Glycolysis is a metabolic pathway in which a 6-carbon glucose molecule is oxidized to result in twopyruvic acid molecules. This glycolytic pathwaymainly produces energy in tissues that remain in alow-oxygen state, e.g. those with low-oxygenatedred blood cells. The catalytic reactions involve theactions of several enzymes, including phosphofructokinase, hexokinase, and pyruvate kinase. Bioactivecomponents from medicinal plants such asdandelion are known to regulate enzymes such ashexokinase, glucokinase, and phosphofructokinase. These enzymes are involved in the processes of glycolysis and the Krebs cycle. Studies have shown that plants rich in CGA can improve the functional activities of these crucial enzymes (phosphofructokinase, hexokinase, and pyruvate kinase).

Hepatoprotective Effects

Antioxidant Effect

Oxidative stress is a common feature observed in a wide spectrum of chronic liver diseases including viral hepatitis, alcoholic, and nonalcoholic steatohepatitis. Oxidative stress leads to deleterious processes in the liver and produces liver diseases. Therefore, restoring antioxidants is essential to maintain homeostasis. One method of restoring antioxidants is suggested to consume natural compounds with antioxidant capacity (Casas-Grajales *et al*.,2015) [4]. Dandelion, a natural antioxidant compound has been empirically used due to its health-promoting properties as an anti-carcinogenic, anti-inflammatory and anti-oxidant (You *et al*., 2010) [36]. Ethanolic *Taraxacumofficinale* leaves and root extract significantly attenuated marker enzymes of liver toxicity, aspartate and alanine transaminases (AST and ALT), lipid peroxidation and oxidative stress induced by acetaminophen in mice. The *Taraxacumofficinale* extract have shown to possess the free radical quenching activities. This protective effects of Taraxacumofficinale have been suggested due to the presence of phenolic compounds in the extract (Colle *et al*., 2012) [6]. In a recent study, ethanolic and n-hexane *Taraxacumofficinale* leaves extract significantly decreased the liver marker enzymes, superoxide dismutase (SOD), catalase, lipid peroxidation and glutathione peroxidase (GPx) in rats intoxicated with CCl_4. The efficacy of *Taraxacumofficinale* ethanolic leaves extract was found to be more effective as compared with n-hexane extract and silymarin against CCl_4 induced hepatotoxicity and oxidative stress in rats (Ahmed *et al*., 2013) [1].

In CCl_4 induced oxidative stress model *Taraxacumofficinale* extract reversed the glutathione (GSH) depletion, up-regulation of Nuclear factor-kB (NF-kB) and increased expression of regulatory inflammatory mediators, such as inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, Tumor necrosis factor- α (TNF-α) and interleukin (IL)-1α (Koh *et al.*, 2010) [12]. These results suggest that

Taraxacumofficinale have a hepatoprotective effect by modulating inflammatory responses and ameliorating oxidative stress. Alcohol is a leading cause of liver disease and is associated with significant morbidity and mortality. Alcohol induced liver diseases represents a spectrum of liver pathology ranging from fatty change to fibrosis to cirrhosis (Dugum and McCullough, 2015) [9]. The protective effects of *Taraxacumofficinale* root against alcoholic liver damage were investigated *In vitro* in HepG2/2E1 cells. In this study, ROS was generated by the administration of ethanol,this was consequent to decrease in cell viability by less than 40%. However, cells were simultaneously treated with ethanol and *Taraxacumofficinale* hot water root extract, did not induce cytotoxicity as compare to ethanol alone treated HepG2/2E1 cells (You *et al.*, 2010) [36].

Antifibrotic Effects

Hepatic fibrosis is common sequel following chronic liver injury and reversal of fibrosis prior it attains the cirrhotic stage would be a clear therapeutic strategy (Lee *et al.*, 2015). *Taraxacumofficinale* extract has been evaluated against the drug and chemical induced hepatic fibrosis in experimental animals and came out with promising results. The study suggested that administration of *Taraxacumofficinale* promote the complete regression of fibrosis and the enchantment of hepatic regenerative capabilities.

Anticancer Activity

Hepatocellular carcinoma (HCC) is one of the most common malignancies, which accounts for 90% of primary liver cancer. HCC usually presents with poor outcomes due to the high rates of tumor recurrence and widespread metastasis (Mao and Wang, 2015) [19]. Recent results pointed out that natural products, in particular those present in *Taraxacum*root extract, have great potential as non-toxic and effective alternatives to conventional modes of chemotherapy available today. Dandelion has been said to induce cytotoxicity in Hep G2 cells and decreases its viability below 40% (You *et al.*, 2010) [36]**.** *Taraxacumofficinale* extract significantly induced the secretion of TNF-α and IL-1 α and apoptosis of Hep G2 cells (Koo *et al.*, 2004) [31]. These strategies are clearly implicated in anticancer efficacy of dandelion. In a very recent study it was found that relevant cytotoxic effect in *T. lacistrum*extract over HeLa and HepG2 cell lines (Mingarro *et al.*, 2015) [20]. However, studies regarding the usefulness of *Taraxacumofficinale* against liver carcinoma experimental models are scanty or not available in literature. Hence, further studies are warranted in animal models to prove the promising anti-cancer efficacies of *Taraxacumofficinale* observed in*in vitro* cancer cell line models *i.e.*, Hep G2 and HeLa.

Inhibitory effect on HIV-1 replication and reverse transcriptase activity

Human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS). This disease represents a huge concern for globalpublic health. Currently, there is no effective vaccinefor HIV-1 (Cohen *et al*., 2007) [5] thus, prevention and antiviral drugs arethe only option to decrease morbidity and mortality inHIV-1-infected individuals. Several classes of antiretroviraldrugs have been developed targeting viral proteinsat different stages of the HIV-1 life cycle or host factors. Virus cell-based fluorescence assay using pseudo typeparticles is an efficient and cost-effective screening systemand has been used for primary screening of novelagents against HIV-19 (Lindsten *et al*., 2001) [17]. Pseudo typed viruses producedin this system can mimic most stages of the HIV-1 life cycle, including viral protein production, assembly, release, maturation, entry, integration and replicationwithout producing replication-competent viruses. Thisapproach has the potential to identify inhibitors againstmultiple viral and cellular functions essential for HIV replication (Kremb *et al*., 2010) [14]. The level of HIV-1 replication has beenassessed by the expression of reporter genes representedby the percentage of GFP-positive cells. Reverse transcriptase assay kit wasused to detect inhibitory effect on RT enzyme activity ofdandelion. These results suggest that dandelion extracthas a potent inhibitory activity against HIV-1 replicationand RT activity.

Conclusion

The findings from literature overwhelmingly revealed that *Taraxacumofficinale* (dandelion) is widely used in traditional and natural medicine systems worldwide. *Taraxacumofficinale* (dandelion) has a significant antioxidant capacity as the leaves are rich in vitamin C, flavonoids and carotenoids. It can be a readily available source of minerals and antioxidants in human diet. Physico-chemical and sensory qualities of dandelion recommend to use its leaves as fresh salad, flowers and roots in acidic dairy or cheese for the content in carotenoids, chlorophyll and fiber that raise the nutritional value and appearance of products**.** Some promising research has been donewith underlying reasons to screen different parts of this herbal plant for their anti-diabetic effect, hepatoprotective effects, antisteatotic effect, antilipidemic and anticancer effects. Dandelion has been credited to be safe with GRAS status. Since, there are currently insufficient data from wellconducted clinical trials so, extensive invitro, in-vivo, and clinical research is required to investigate further the pharmacological, physiological, and biochemical mechanisms underlying the health promoting effects of dandelion to promote its usage for therapeutic purposes.

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