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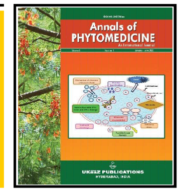

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Herbs that heal: The philanthropic behaviour of nature

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Abstract

The ancient world practically depended on herbal sources of medicines to treat common as well as chronic diseases. Till now, over 80% population in the developing and under developed countries depend on plant materials for the same. Many claims have been justified about the efficacy of modern medicines; it is interesting to know that most of them are derived from plants. The common herbs and spices are exploited by the existing herbal branches of medicines to prepare potential drugs. Occasionally, it also uses rare species of medicinal plants, native to specific climate or region. The screening of new and rare plant species is required to improve the scope of pharmacological alternatives. However, the common herbs and spices provide a more practical, productive as well as a feasible source of medicine. Hence, the current review describes the medicinal benefits of black cumin (*Nigella sativa* L.) and celery (*Apium graveolens* L.) seeds, and chicory (*Cichorium intybus* L.) roots. They are not only commonly available but are loaded with essential nutrients that promote overall health and boosts immunity.

1. Introduction

Plants are basic yet essential provenances of food, shelter, fertilisers, textile and natural pigments, among others. The medicinal importance of plants have also been realised and practised exclusively for the treatment of known diseases by ancient human civilizations. Most of these practices evolved through different cultures, and have now been established as herbal medicinal systems. Some of these systems are unique to different parts of the world, *e.g.*, the Chinese traditional medicine system and the Indian Ayurveda. The Chinese herbalism is one of the most prevalent branches of medicine, and is established on the principles of balancing the concepts of yin (cooling), yang (stimulating) and *Qi* (life force) energy (Motaleb, 2011). Similarly, the Indian Ayurveda preaches steadiness between mind, body and spirit (Dominic, 2003). Statistically, over 80% of the global population uses similar plant-based herbalist approach as their primary form of healthcare (Boakye *et al*., 2015).

Recent times have acknowledged the necessity of sustainable sources of a variety of compounds including medicines, to prevent the harmful effects of synthetic drugs. There are several underutilized and unexplored food plants in nature. The studies characterizing their nutritional, antinutritional or therapeutic potential will not only help us in overcoming the side effects of synthetic drugs but also help us to fight malnutrition, especially among underprivileged population groups (Memariani *et al*., 2020). The medicinal plants are rich sources of essential phytonutrients that show a wide range of therapeutic effects (Ansari and Ahmad, 2019). Moreover, the leaves, fruit, roots, stem, tubers and/or bark of the same plant may be effective against different diseases due to the presence of different active ingredients. However, thorough knowledge of these plants is essential, because there are studies that report the medical significance of one part of the plant whereas the toxic effect of other parts of the same plant (Van Wyk, 1997).

Over the years, modern medicine has evolved by commercializing the production of several effective drugs. However, the plant sources remain the backbone of medicinal products. Few examples include paclitaxel derived from *Taxus brevifolia* (Wheeler *et al*., 1992), aspirin from the bark of Willow tree, morphine from the opium poppy, digoxin from foxglove, quinine from cinchona bark (Vickers *et al*., 2004), artemisinin from *Artemisia annua* (Numonov *et al*., 2019), silymarin from *Silybum marianum* (Abenavoli *et al*., 2018) and forskolin from *Coleus forskohlii* (Loftus *et al*., 2015).

In spite of the successful allopathic practices, there is an increasing demand for herbal products which is apparent from its 5 billion dollar market in the U.S alone (Shalini *et al*., 2013). Hence, it can be contemplated that the herbal medicine system is here to stay. Apart from the harmful effects of prolonged use of allopathic medicines,

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the main reason for the growing interest in herbal medicines can be contributed to factors like cultural acceptability, better compatibility as well as the feasibility of these products. Also, the traditional knowledge is more accessible, reliable and trusted by common people all over the world (Vidyarthi *et al*., 2013).

The herbalist approach is certainly beneficial. However, there are few easily avoidable drawbacks of the herbal system of medicines. For instance, most herbalists formulate a specific drug recipe depending on their own experience, practise, observations and knowledge. The system severely lacks uniformity, documentation and maintenance. In order to truly evolve as an alternative to modern medicine, a standard scientific protocol is required along with vigorous clinical validation to analyse and document the efficacy of herbal products (Kamboj, 2000).

In the current review, the medicinal properties of 3 common plant/plant products, *i.e.*, black cumin (*Nigella sativa* L.) and celery (*Apium graveolens* L.) seeds, and chicory (*Cichorium intybus* L.) roots are reviewed. These plants contain diverse micro-nutrients that help in improving the immune system. Moreover, they have immense economic value. For instance, Belgium and Netherland together produced over 77% of *C. intybus*, in 2011. Since, then it is emerging as the primary market for herbal medicines (Samantha, 2018). According to the National Horticulture Board (NHB), India exported over 5000 million tons of celery seed oil in 2000-01, which is worth 1.7 billion rupees.

2. Black cumin (*Nigella sativa* L.)

Nigella sativa L. is a flowering plant that grows up to 20-90 cm. It is an annual plant and belongs to the family Ranunculaceae. The plant produces finely divided leaves with thread-like segments, and coloured flowers (varied shades of blue, purple, white, yellow and pink) with five to ten petals (Figure 1). The fruit is capsule shaped with several follicles that contain black seeds. Originally it was grown in regions of South Europe, North Africa and Southwest Asia. However, it is now cultivated in many countries throughout the world (Ahmad *et al*., 2013).

Figure 1: Black cumin plant, seeds and oil (Adapted from Eid *et al*., 2017).

The unique chemical composition of *N. sativa* seeds has particularly led to its extensive investigation for therapeutic purposes. The chemical compounds in *N. sativa* seeds impart a bitter taste to it. The chemical composition, as well as the bitterness, may differ with soil type, season and age of plant (Bulca, 2015). It contains a rich and diverse composition of various nutrients represented in Table 1. Most of the therapeutic effects of *N. sativa* seed are due to thymoquinone. Several studies have reported beneficial immunologic and curative properties of this compound (Forouzanfar *et al*., 2014). Although, *N. sativa* seeds are potentially known to treat of many diseases, several on-going researches are specifically focussed towards the treatment of cancer, diabetes and cardiovascular disorders.

Table 1: Chemical composition of *N. sativa* seeds (Bulca, 2015; Forouzanfar *et al*., 2014)

Biochemical components	Content
Unsaturated fatty acids (32-40%) consisting of	
Linoleic acid	50-60%
Oleic acid	20%
Eicodadienoic acid	3%
Dihomolinoleic acid	10%
Saturated fatty acids (14-15%) consisting of	
Palmitic and stearic acid	30%
α-sitosterol	44-54%
Stigmasterol	6.57-20.92%
Essential oil (0.5-1.6%) consisting of	
Thymoquinone	30%-48%
Thymohydroquinone, dithymoquinone, p-cymene	7%-15%
Carvacrol	6%-12%
α-thujene	5.6%
4-terpineol	2%-7%
Longifolene	2%
t-anethol	1%-4%
Sesquiterpene longifolene	1%-8%
α-pinene and thymol	Less than 1%
Proteins	16-20.85%
Carbohydrates	31-33.9%
Fibre	5.5-7.94%
Total ash	4.8%
Alkaloids, tannins, carvone, limonene, citronellol, resin, amino acids, vitamin A and minerals like Cu, P, Zn and Fe	Trace amounts
Other vital biochemicals reported	
Nigellone, stigmastanol, stigmasterol-7-ene, β-amyrin, butyro-spermol, cycloartenol, hederagenin, terpenoids, aliphatic alcohol, β-unsaturated hydroxy ketone, hederagenin glycoside, melanthin, melanthigenin.	

2.1 Cardiovascular disorders

Cardiovascular disorders are a major health concern and have a significant fatality rate worldwide. The changes in lifestyle have gradually increased the prevalence of obesity which has in-turn increased the incidences of hypertension, atherosclerosis, and hypercholesterolemia. These factors collectively contribute to cardiovascular diseases. The cardio-protective effects of *N. sativa* are believed to work centrally by direct or indirect involvement of serotoninergic and muscarinic receptors that regulate blood pressure (Leong *et al*., 2013).

Shabana *et al.* (2013) reviewed over 100s of relevant articles published between 1960 and 2012 and reported the beneficial effects of *N. sativa* seeds in the treatment of cardiovascular disorders. Most of the reported studies have highlighted the multifunctional potential of *N. sativa* seeds to act as an antioxidant, antiinflammatory, hypotensive, diuretic and immunomodulatory agent, as the reason for effective treatment of cardiovascular disorders. Positive effects of *N. sativa* seeds are reported against cardiotoxicity, atherosclerosis, endothelial dysfunction, arterial pressure, hypercholesterolemia and platelet aggregation. A recent study demonstrated that prolonged administration of *N. sativa* seed extracts may have coronary angiogenic effect on lab rats. The study reported an increase in the production of vascular endothelial growth factor and a decrease in the production of Von Willebrand factor, thus indicating that *N. sativa* extracts may potentially prevent and cure ischemic heart disease (Al Asoom, 2017). Thymoquinone also relaxes the smooth muscles by activating the ATP-sensitive potassium channels and blocking the serotonin, alpha1 and endothelin receptors non-competitively. Moreover, these biochemical reactions effectively improve with the increase in concentration of thymoquinone (Suddek, 2010). It has also shown a significant reduction in the plasma levels of triglycerides, cholesterol, LDL and an increase in HDL (Shakeri *et al*., 2018).

2.2 Antidiabetic and antiobesity activity

Diabetes is another metabolic disorder, whose prevalence is increasing rapidly due to lifestyle changes. Although, the management of diabetes mellitus is possible, its complete treatment is not reported in the literature. Moreover, the harmful effects of prolonged use of antidiabetic medications, and other limitations have led to the exploration of alternative treatment methods (Daryabeygi *et al*., 2017).

A partial recovery of hepatic glycogen and regeneration of pancreatic islets, by *N. sativa* hydro-alcoholic extracts (5 mg/kg b.w.), have been reported (Alimohammadi *et al*., 2013). The aqueous extracts of *N. sativa* significantly decreased glycemia and restored insulinemia in diabetic rats (Touati *et al*., 2017). They also reported significantly reduced triglycerides, cholesterol and LDL levels, and increased HDL levels, thus indicating the efficacy of *N. sativa* to manage diabetes and obesity. The efficacy of *N. sativa* oil in overcoming insulin resistance is also documented (Najmi *et al*., 2008). A recent study carried out on diabetic rats reported that the essential oil of *N. sativa*, at 2 mL/kg concentration, significantly reduces plasma glucose level during fasting and boosts insulin levels. Moreover, the diabetic rats showed improvements in their lipid profile as well as the islets cell count (Abdelrazek *et al*., 2018). Interestingly, the *N. sativa* seed extracts also show a potential to significantly decrease the formation of early and advanced glycation products and reverse the glycation-induced DNA damage (Pandey *et al*., 2018). A further study carried out using thymoquinone, instead of crude *N. sativa* extract showed even better activity against the formation of above products. The glycation-induced aggregation of BSA was significantly reduced, and a reversal activity was noted in glycoxidative damage of DNA (Kumar and Ali, 2019). Thymoquinone is reported to be a therapeutically effective agent for controlling diabetes since it accentuates the glucose-induced secretion of insulin and prevents glucose absorption from the intestinal mucosa (Kapoor, 2009). They further decrease the oxidative stress and inflammatory responses which helps in effective control of lifestyle disorders like diabetes and obesity (Kapoor, 2009).

Mahdavi *et al.* (2016) investigated the effects of supplementation of essential oils of *N. sativa* with a low-calorie diet to effectively control obesity. They reported better management of weight and inflammatory status in obese women using a parallel-randomized design. The change in body composition and circulating adipokines has also been reported on the intake of essential oils of *N. sativa*.

2.3 Anticancer activity

The *N. sativa* seeds have gained more interest among the scientists during the last 2 decades. Thymoquinone, an active component of *N. sativa* seeds, has particularly proven useful for the treatment of cancers of blood, breast, colon, liver, lung and prostate. Thymoquinone exhibits anticancer activity by acting as a potent immunomodulatory and antimutagenic agent. They are further reported to increase the activities of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase which are beneficial against different types of cancer. Besides, they interfere with DNA structure of cancer cells and affect the carcinogenic signalling molecules (Khader *et al*., 2010). The safety of thymoquinone has been confirmed based on animal studies (Al-Ali *et al*., 2008).

The potential implication of thymoquinone in the prevention and treatment of tumour and cancer of breasts may be due to the regulation of the PPAR-γ activation pathway. The pro-apoptotic action of thymoquinone is also reported against colon cancer cell line HCT116 (Woo *et al*., 2011). The supplementation of *N. sativa* has also been shown to significantly reduce tumour development and cellular proliferation in the lungs, alimentary canal, pancreas and the esophagus (Salim, 2010). Khan *et al.* (2011) reported a prophylactic effect of thymoquinone against chemical carcinogenesis due to the increased activity of glutathione transferase and quinone reductase on its oral administration. Similar activities were also observed against toxicity in hepatic cancer.

2.4 Immunomodulatory activity

The probable therapeutic implications of the immunomodulatory activity of *N. sativa* in prophylactic treatment of patients suffering from cancer and opportunistic infections have been confirmed by Ghonime *et al.* (2011). Boskabady *et al.* (2011) reported that the lung inflammation can be prevented by *N. sativa* extract by using guinea pigs sensitized by ovalbumin as an experimental model. Another study demonstrated significant improvement in immune parameters in murine ovalbumin induced allergic diarrhoea in mice, on treatment with *N. sativa* seed extracts as well as thymoquinone. The extracts exhibited anti-inflammatory response by decreasing the number of mast cells and mast cell protease-1 in intestines and plasma of mouse respectively (Duncker *et al*., 2012). A similar study reported a reduction of inflammatory mediators and increased immune response on administration of thymoquinone, for treatment of arthritis that was induced using collagen in rats (Ahmad *et al*., 2013). Similarly, the efficacy of *N. sativa* in treatment of hyperoxia-induced lung injury has been reported using rats as models (Tayman *et al*., 2012). Both studies indicated a significant decrease in the severity of lung injury on administration of *N. sativa* essential oils.

2.5 Other activities of Black cumin

Black cumin seed is considered as a “miracle seed” and holds significant importance in the Unani system of medicine practised mostly in Islamic countries of South Asia and Central Asia. It shows a wide range of properties including antibacterial, antifungal, antiviral, anthelmintic and antiparasitic against *Schistosoma mansoni* (Ahmad *et al*., 2013).

There are reports of the specific activity of *N. sativa* extract against asthma (Koshak *et al*., 2017) and rheumatoid arthritis (Tekeoglu *et al*., 2007) due to its inhibitory effect on mast cells to produce histamine and antioxidant activity (Bordoni *et al*., 2019). *N. sativa* extracts are also effective against gastro-intestinal problems and work by acting as a digestive stimulant (Platel and Srinivasan, 2001), appetite stimulant (Ahmad *et al*., 2013) and antiulcer agent (Rajkapoor *et al*., 2002). The hepatoprotective (Farrag *et al*., 2007), neuroprotective (Akhtar *et al*., 2012) and respiratory protective (Koshak *et al*., 2017) activity of *N. sativa* extracts are also reported. It is also effective in skin disorders like psoriasis (Okasha *et al*., 2018), acne (Hadi and Ashor, 2010), burns (Yaman *et al*., 2010), wounds (Abu-Zinadah, 2009) and vitiligo (Sarac *et al*., 2019) due to the combined healing properties like analgesic, antioxidant and antiinflammatory.

Apart from above properties, thymoquinone effectively stimulates milk production (Goreja, 2003), improves memory (Sahak *et al*., 2016), prevents anxiety and convulsion (Akhtar *et al*., 2012), and corrects the male infertility problems (Kolahdooz *et al*., 2014). It also possesses antitussive (Hosseinzadeh *et al*., 2008), diuretic (Rajsekhar and Kuldeep, 2011) and spasmolytic (Keyhanmanesh *et al*., 2014) properties.

3. Celery (*Apium graveolens* L.) seeds

Agave graveolens L. is a branched, furrowed, succulent, and rigid plant with pinnate leaves that belongs to the family Apiaceae. It produces small creamy-white flowers and approximately 2 mm long ovoid to globose seeds (Figure 2). It was originally cultivated as a food plant in European countries like Italy and France. Later on, it was widely grown in regions of Sweden, Algeria, Egypt, Ethiopia and Saudi Arabia (Fazal and Singla, 2012).

Figure 2: Celery plant, flower and seeds (Adapted from Hussain *et al*., 2013).

Table 2: Chemical composition of *A. graveolens* seeds (Sastri, 1949)

Biochemical components	Content
Unsaturated fatty acids (64.10%) consisting of	
Petroselinic acid	64.3
Linoleic acid	18%
Linolenic acid	0.6%
Oleic acid	8.1%
Eicodadienoic acid	3%
Dihomolinoleic acid	10%
Saturated fatty acids (5.8-14.2%) consisting of	
Palmitic acid	6.9%
Stearic acid	1.4%
Hexadecenoic acid	0.1%
Essential oil	1.5-3%
Proteins	0.8%
Carbohydrates	35.7%
Fibre	20.7%
Total ash	6.9-11%
Moisture	5-11%
Phthalides	3-5%
Furocoumarins, vitamins, tannin	Trace amounts
Other vital biochemicals reported	
Caffeic acid, catechin, catechol, chlorogenic acid, chrysin, rosmarinic acid, ellagic acid, ferulic acid, gallic acid, *p*-coumaric acid, protocatechuic acid, pyrogallol, salycilic acid syringic acid, *cis*-vaccenic acid, sedanolidesedanonic anhydride, 3-*n*-butyl phthalide, and other minor phthalides.	

The seeds of this plant are mainly used in herbal drug formulations medicinal purposes and are commercially available in the market. It has an aromatic taste due to the presence of sedanonic anhydride and sedanolide (Gauri *et al*., 2015). It also contains caffeic acid, chlorogenic acid, apiin, apigenin, rutaretin, ocimene, bergapten, and isopimpinellin as main constituents (Sastri, 1949). A detailed composition of *A. graveolens* seeds is represented in Table 2. Traditionally, celery was used commonly for the treatment of spasm and stomach problems due to its diuretic, laxative, and sedative properties. However, recent researches have indicated its possible healing properties in cardiovascular disorders and joint problems (Al-Asmari *et al*., 2017).

3.1 Cardiovascular disorders

Celery seed extract potentially regulates the prostaglandin levels and hence indirectly regulates the blood pressure and cholesterol levels. It may also inhibit the biosynthesis of cholesterol in liver or reduce the absorption of lipid in the intestine. Also celery extracts may increase the excretion of fecal bile acids and enhance the lecithin-cholesterol acyltransferase activity in plasma. These factors further help in maintaining a healthy cardiovascular system (Ahmed and Sayedda, 2012). An active hypertensive compound, n-butylphthalide, is identified from *A. graveolens* seeds. This compound was reported to regulate the blood pressure in control rats as well as those treated with deoxycorticosterone acetate to induce hypertension. A study reported better activity of 300 mg/kg of hexane extracts of celery seeds to be 3.7 and 4 times more effective than methanolic and aqueous-ethanolic extracts in regulating the blood pressure (Moghadam *et al*., 2013). This was due to the higher concentration of n-butylphthalide in hexane extracts. *A. graveolens* leaf extracts (200 mg/kg) possess hypotensive and lipid lowering effects by regulating the blood pressure, cholesterol, triglyceride and lipopolysaccharides (Dianat *et al*., 2015). The phthalides present in celery results in expanding of smooth muscle in the blood vessels which helps in decreasing the blood pressure. Moreover, the antioxidative and anti-inflammatory properties of phthalides provide additional protection against cardiovascular diseases, especially atherosclerosis (Hedayati *et al*., 2019).

3.2 Antidiabetic and antiobesity activity

In general, the celery seed extracts significantly reduces the levels of glucose in serum and induces the pancreatic islets to release insulin (Niaz *et al*., 2013). A significant reduction in triglycerides, cholesterol and LDL levels has been reported by Tsi *et al*. (1995) on obese rats, on the administration of celery extracts. A reduction in activation of triacylglycerol lipase and increase in microsomal P450 was observed in the liver of their experimental model. Luteolin, a compound found in celery, significantly decreases the acetylation of p65 and activation of NF κB activation. It also allows the expression of histone acetyltransferase and its interaction with NF κB in macrophages. Moreover, it attenuates the oxidative stress in cardiac muscles and show protective effect on diabetes mellitus and cardiac dysfunction (Kim *et al*., 2014). Luteolin may also be responsible for stimulating insulin production in 3T3 L1 adipocytes to increase the uptake of glucose. This may be achieved by enhancement of serine/threonine protein kinase phosphorylation and the role of luteolin in insulin signalling cascade. It may be further involved in reducing mRNA levels of interleukin-6, tumor necrosis factor alpha and monocyte chemoattractant protein-1 that are related to insulin resistance and obesity (Ding *et al*., 2010). In another study, Wang *et al*. (2012) reported a significant reduction in the serum triglycerides, cholesterol, malondialdehyde, creatin kinase, lactate dehydrogenase, superoxide dismutase and Akt phosphorylation levels on intake of celery seed extracts. Another component of celery, apigenin, has also shown a significant antihyperglycemic effect by increasing the insulin levels in serum of diabetic rats (Panda and Kar, 2007).

3.3 Anticancer activity

Apigenin is among the most abundant flavonoids found in nature, which also shows anticancer properties. It is present in common fruits and vegetables including celery seeds (3000-5000 μg/g), vinespinach (786.5 μg/g) and chinese celery (240.2 μg/g). Birt *et al*. (1986) were the first to demonstrate the efficacy of apigenin against mutations and cancer cell proliferation. Since then, extensive research has been carried out on various animal models to study the anticancer property of this compound. It is suggested that apigenin may be directly involved in induction of apoptosis, or it may indirectly stimulate other pro-apoptotic factors in cancer cell lines of oral (Masuelli *et al*., 2011), esophageal (Zhang *et al*., 2008), colorectal (Turktekin *et al*., 2011), hepatic (Khan *et al*., 2006), and pancreatic cancers (Lee *et al*., 2007).

A recent study reported the inability of cancer cells to efficiently utilize glucose in presence of apigenin. It may also inhibit the remodelling of extracellular matrix and prevent the development of blood vessels that support the growth of tumours (Kowalczyk *et al*., 2017). The administration of apigenin orally, in concentrations of 20 and 50 μg/mice, for 20 weeks is reported to reduce tumour volumes in mouse prostate by suppressing phosphoinositide 3-kinase (PI3K)/Akt/Forkhead box O-signalling pathway. It was also found to abolish distant organ metastasis in the transgenic adenocarcinoma of a mouse prostate model (Shukla *et al*., 2014).

3.4 Immunomodulatory activity

Celery seeds contain several essential phytochemicals like phenolic acids, flavones, flavonols, and antioxidants, beta-carotene and manganese. Thus, they contribute to overall immunity mainly by acting as antioxidative and antiinflammatory agent (Hedayati *et al*., 2019). *A. graveolens* seeds showed a protective effect against LDL-induced injury of macrophages by decreasing the secretion of cytokine TNF-α and interleukin (IL)-6 and suppressing the production of NF-κB, p65 and notch1 protein expressions (Si *et al*., 2015). Apigenin is a flavonoid component of celery leaves and seed that stimulates the activity of antioxidant enzymes and, thereby decreases the oxidative damage to tissues (Lugasi *et al*., 2003). It also reduces lipid peroxidation by increasing the concentration of reduced glutathione (Kolarovic *et al*., 2009).

3.5 Other activities of celery

Besides the above mentioned medicinal effects, celery seeds were traditionally used to treat gastric problems, and as a heart tonic (Fazal and Singla, 2012). The seeds as well as leaves of celery are used as a libido stimulant in herbal medicine and for amplification of the sperm profile (Kerishchi *et al*., 2011). This is believed to be due to the antioxidative action of celery that has an impact on the hypothalamic-pituitary-testicular axis that regulates the above activities. Consistent intake of celery seeds also increases the secretion of breast milk (Hardani *et al*., 2015). It is also effective against jaundice (Nadkarni, 2010), psoriasis, (Khare, 2007) and colic (Kritikar and Basu, 2008).

Other healing properties of celery include antifungal, antipyretic, antiinflammatory (Fazal and Singla, 2012), hepatoprotective (Nadkarni, 2010), mosquito repellent (Kumar *et al*., 2014), antibacterial, anti-spasmolytic (Naema *et al*., 2010), analgesic and antiulcer (Fazal and Singla, 2012).

4. Chicory (*Cichorium intybus* L.)

Cichorium intybus L., commonly known as chicory, is an erect fairly woody perennial herb, around 1m in height that belongs to the family Asteraceae (Figure 3). It has a fleshy taproot system of up to 75 cm in length and large basal leaves (Chauhan, 2019). It was originally grown by the ancient Egyptians as a medicinal plant and coffee substitute (Street *et al*., 2013). The roots of chicory plant are beneficial for the treatment of various disorders, particularly diabetes, due to the presence of inulin in high concentrations. It was discovered in the 1970s and since then it is exploited as a means of diabetes control agent (Van Arkel *et al*., 2012).

Figure 3: Chicory seeds, flowers and roots (Adapted from Nwafor *et al.*, 2017).

Although, the roots are mainly used as a source of medicine, the leaves can be used in salad dressing and contain several beneficial compounds. *C. intybus* shows presence of over 100 active components including tannins, saponins, flavonoids, terpenoids, cardiac glycosides and anthocyanins, with majority of them present in roots. The roots are generally bitter and contain over 68% inulin. In addition, it also contains coumarins, flavonoids, sesquiterpene lactones (lactucin and lactucopicrin), tannins, alkaloids, vitamins, minerals, and volatile oils, as represented in Table 3. Apart from being an antinutritional agent, it is also reported to be extremely effective in eliminating intestinal worms from livestock (Nwafor *et al*., 2017).

Table 3: Chemical composition of *C. intybus* roots (Nwafor *et al*., 2017)

Biochemical components	Content
Inulin	68%
Other carbohydrates	21%
Sucrose	14%
Cellulose	5%
Proteins	6%
Fibre	5-6%
Total ash	4%
Tannins, saponins, flavonoids, terpenoids, cardiac glycosides and anthocyanins	2-3%
Minerals like Ca, K, Mg, Na	1%
Micronutrients like Fe, Cu, Mn, Zn	Trace amounts
Other vital biochemical reported	
Vanillin, pyrazines, phenols, organic acids, ß-carbolines, triterpenes, flavonoids, latex, tannins, and saponins, benzo-isochromenes, tannins, palmitic acid, linoleic acid, pectin and choline.	

4.1 Cardiovascular disorders

As mentioned earlier, caffeine-free chicory coffee, prepared using its roots, is a rich source of phenolic compounds. The caffeic acid, in particular, inhibits *in vitro* platelet aggregation, phenylpyruvate tautomerase enzymatic activity of the proinflammatory cytokine and serum macrophage migration inhibitory factor. Caffeic acid also significantly reduces whole blood and plasma viscosity. The combined effect of caffeic acid with other phenolic compounds was suggested to have antithrombotic and antiinflammatory effects (Schumacher *et al*., 2011).

A study on toad heart, after administration of *C. intybus* root extracts, indicated an antiarrhythmic action that was determined by blocking the ganglia and after atropinisation (Balbaa *et al*., 1973). A study carried out on laboratory rats showed significant vasorelaxant activity of *C. intybus* extracts against contractions of the aorta which was induced by norepinephrine. The study further indicated that these contractions may be due to restricted influx of calcium from the extracellular space (Sakurai *et al*., 2003). The ethanolic extracts of *C. intybus*, at a dose of 500 mg/kg b.w., showed detoxification activity in cisplatin - induced toxicity on electrolyte balance in rats. The activity of *C. intybus* counter acted the electrolytes imbalances and Na^+ K^+ ATPase activity on pre-treatment (Noori and Mahboob, 2012). The myocardial infarction was also significantly reduced in size, in hearts perfused by 3 mg/ml *C. intybus* extract. Moreover, considerable improvement in heart rate, blood pressure and coronary flow were observed during reperfusion by the above extract in male Wistar rats (Sadeghi *et al*., 2015).

4.2 Antidiabetic and antiobesity activity

C. intybus roots are largely composed of inulin-type fructans. It is a naturally occurring polysaccharide that belongs to the class of dietary fibres. Substantial data is available in literature that suggests that chicory inulin improves glucolipid metabolism by activating insulin receptor substrate and suppressing the c-Jun N-terminal kinase and mitogen-activated protein kinase pathways. This mediates a metabolism-modulatory effect like antihyperglycemic and antidyslipidemic in patients with type 2 diabetes mellitus (Ning *et al*., 2017). Besides, caffeic acid and chlorogenic acid also stimulates insulin secretion from islets of Langerhans. Also, chicoric acid exhibits both insulin-sensitizing and insulin-secreting properties (Tousch *et al*., 2008)

The level of adiponectin and HbA1c values show significant improvement on the administration of *C. intybus* root extracts, and thus suppresses the elevation of postprandial blood glucose levels (Nishimura *et al*., 2015). In addition, the *C. intybus* extracts cause a direct modulation of cytokine expression resulting in anti-inflammatory response (Rezagholizadeh *et al*., 2016). These observations suggest that the early onset of diabetes mellitus can be prevented or delayed by using *C. intybus* root extracts.

An experimental model was set up to study the antidiabetic and antiobesity properties of *C. intybus* ethanolic extracts on obese diabetic rats. The extracts not only resulted in lowering of blood glucose levels but also significantly reduced the triglyceride, total cholesterol and LDL. It also showed an elevated level of HDL. The study further reported a considerable increase in reduced glutathione, superoxide dismutase, glutathione-S-transferase and catalase, and a decline in malondialdehyde level. This indicates that *C. intybus* extracts prevent diabetes complications, including obesity, by regulating the oxidative stress system (Samarghandian *et al*., 2013). Additional properties of *C. intybus* leaf extracts like anticholinesterase activity, decrease in brain lipopolysaccharide and increase in catalase activity have also been reported (Ahmad *et al*., 2009).

4.3 Anticancer activity

Magnolialide, a 1β-hydroxyeudesmanolide which is a component of *C. intybus* roots effectively inhibits tumour cell lines (Lee *et al*., 2000). *C. intybus* extracts also show promising outcomes in the treatment of neoplastic disorders (Zaid *et al*., 2012). The *C. intybus* roots and leaf extracts have shown to have significant inhibitory and antiproliferative effect on Ehrlich tumour carcinoma in mice (Hazra *et al*., 2002) and amelanotic melanoma C32 cell lines (Conforti *et al*., 2008), respectively. In particular, hydroxybenzoic and hydroxycinnamic phenolic acids found in red chicory (*Cichorium intybus* L. cultivar) has been demonstrated to induce strong antiproliferative effects and apoptosis in human colon cancer cells (Brown *et al*., 2012). The inhibition of different cancer cell line has further suggested its possible role as chemopreventive agents (Tramer *et al*., 2012). A recent study has identified several novel compounds like guaianolides, 6 methoxyflavone, eudesmanolides, germacranolides, polyacetylene, sterol, anthocyanin, delphinidin and 3,4 dihydroxyphenethyl that showed in *in vitro*, and antitumor action *in vivo* and clinical trials (Imam *et al*., 2019). Hence, there is a possibility of development of a potential antitumor drug in the near future using *C. intybus* plant.

4.4 Immunomodulatory activity

The ethanolic extracts of *C. intybus* roots have been reported specifically for its immunomodulatory effects. They are rich in natural antioxidants and likely induce overexpression of genes encoding antioxidant enzymes. The administration of *C. intybus* root extracts attenuated CCl4-induced hepatocellular injury in a recent study. It was postulated that the reactive free radical scavengers and the endogenous antioxidant defense system may have been involved in boosting the above reaction (Heibatollah *et al*., 2008). Low concentrations of *C. intybus* also increase IL-12 production by dendritic cells and modulate cytokine release of T cells toward a Th1 pattern. However, it does not change the expression of CD40, CD86 and MHC-II molecules, which are important co-stimulatory markers of dendritic cells. Thus, although *C. intybus* extracts do not promote the maturation of dendritic cells, they can be used in the treatment of various immune disorders (Karimi *et al*., 2014). A considerable restoration of immunity markers like secondary IgG antibody production, phagocytic activity, circulating leucocytes, NK cell activity, cell proliferation, and production of interferon-γ was observed in immune-compromised rat models injected with ethanol extract of *C. intybus* roots. Moreover, there was an improvement in hemagglutination titer, plaque forming cells of spleen and delayed-type hypersensitivity reaction observed in these rats (Kim *et al*., 2002). The β-sitosterol, from *C. intybus* roots, has been identified as an agent that inhibits hyaluronidase and collagenase and shows considerable antiinflammatory and antioxidant effects. Hence, it displays a wound healing effect (Suntar *et al*., 2012). *C. intybus* roots has also shown a dose dependent decrease in edema by diminishing the serum TNF-α, IL-6, and IL-1 levels, attenuating the malonylaldehyde levels and increasing the catalase and glutathione peroxidase activity in albino rats (Rizvi *et al*., 2014).

4.5 Other activities of chicory

The root, stem as well as leaves of *C. intybus* are effective as a blood purifier (Loi *et al*., 2005) and in the treatment of jaundice (Van Wyk, 1997). The secondary metabolites like flavonoids, tannins, and coumarins of *C. intybus* acts as antibacterial (EMA, 2013), antifungal (Badakhasann and Bhatnagar, 2019), antihelminthic (Foster *et al*., 2011), antimalarial (Bischoff *et al*., 2004), antioxidant (Heimler *et al*., 2009), gastroprotective (Gurbuz *et al*., 2002), hepatoprotective (Elgengaihi *et al*., 2016), antiinflammatory (Cavin *et al*., 2005), analgesic (EMA, 2013) and antirheumatic (Mardani-Nejhad *et al*., 2012) agents. It is also effective as an appetite stimulant and against upset stomach, constipation, hemorrhoids (EMA, 2013), ulcer, gallstones (Thorat and Raut, 2018), kidney stones (Emamiyan *et al*., 2018) and gout (Wang *et al*., 2019). Other properties of *C. intybus* roots includes healing of cuts, bruises and wounds (EMA, 2013), strengthening the prostate and other reproductive organs (Al-Shafi, 2016).

5. Conclusion

Black cumin seeds are widely acknowledged for its medicinal properties and are used in various herbal medicinal preparations. The celery seeds and chicory roots were previously used for the treatment of mild symptoms of various diseases. Recent studies and phytochemical analysis have highlighted cardio-protective, antidiabetic, anticancer as well as immunomodulatory properties of these plant products described in this review. Besides, several other medicinal benefits of these plants are also reported. The potential of herbal medicines to be used as drugs is, hence, undeniable. However, the major challenge, in practising herbal based remedies, is the optimization of extraction protocols for efficient recovery of diverse phytonutrients. This is mainly difficult due to the fact that the phytonutrient content depends on several factors like the location of the plant, soil-type, harvest time, harvested part of the plant, and environmental conditions like moisture content. Hence, the current knowledge still requires proper refining basically through data mining and documentation. The clinical trials and other studies may further authenticate their use as alternative medicines.

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Conflict of interest

The author declared that there is no conflicts of interest in the course of conducting the research. The author has final decision regarding the manuscript and decision to submit the findings for publication.

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