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Centratherum anthelminticum (L.) Kuntze a Potential Medicinal Plant with Pleiotropic Pharmacological and Biological Activities

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Abstract: *Centratherum anthelminticum* is an ethnomedicinal plant in India and a common ingredient in Ayurvedic medicine. To date, many scientific studies have been carried out, but a comprehensive review on this plant is lacking. This review aims to cover the biological activities and the active compounds derived from *C. anthelminticum*. Exploration of more than 40 papers available in literature (up to 20th of April 2013) revealed that the pharmacological effects of *C. anthelminticum* range from anti-oxidant, anti-diabetic, anti-microbial to recently found anti-cancer property. Over 120 compounds consisting of fatty acid, sterols, sesquiterpene lactones, flavonoids and carbohydrates have been identified from different parts of the plant. Many of these active compounds were derived from the seeds and have been evaluated for a variety of biological activities. Despite the encouraging results demonstrated by these studies and the traditional use as nutraceutical agent, clinical trials of *C. anthelminticum* extracts or derivatives are absent. Thus, a systematic documenting review would provide more insights and spur further research that would lead to production of safer and economical alternative medicine from *C. anthelminthicum*.

Key words: *Centratherum anthelminticum*, anti-diabetic, anti-cancer, anti-inflammation, anti-microbial

INTRODUCTION

Centratherum anthelminticum (L.) Kuntze is an ethnomedicinal plant commonly grown in India and Southeast Asia. It is a member of Asteraceae family of the flowering plants. *Vernonia anthelmintica* and *Conyza anthelmintica* are scientific synonyms of this plant. Locally, the plant is known as black/bitter cumin, or kalijiri in India. The plant is an erect, pubescent, annual herb which can grow up to 90 cm in height. The leaves of the plant are elliptic-lanceolate, 5 to 9 cm long and 2.5 to 3.2 cm wide. The apex of the leaves is acute, base tapering into the petiole, margins coarsely serrate and pubescent on both surfaces. It has homogamous purple florets, which can be found as solitary, axillary or terminal heads. The seeds are brownish in color, with a hot sharp taste and astringent properties (Rastogi *et al*., 1995; Mehta *et al*., 2004; Bhatia *et al*., 2008a; Ani and Naidu, 2011). It is widely used as folk medicine for diabetes in Rayalaseema, India and a popular ingredient in Ayurvedic medicine. In other places, *C anthelminticum* has been traditionally applied as anthelmintic, stomachic, digestive, diuretic, tonic, alterative, anti-phlegmatic, anti-asthmatic, anti-phlegmatic treatment, as well as a therapeutic agent for cough, diarrhea, helmint, skin diseases, ulcers, leucoderma and fevers (Nadkarni and Nadkarni, 1955; Chopra *et al*., 1956; Kirtikar and Basu, 1987; Nagaraju and Rao, 1989; Amir and Chin, 2011; Arya *et al*., 2012a).

To the best of our knowledge, experimental investigations on the extracts or pure compounds isolated from the plant indicated a vast variety of pharmacological effects, including anti-inflammation/anti-pyretic (Purnima *et al*., 2009; Ashok *et al*., 2010), anti-helminthic (Iqbal *et al*., 2006), anti-viral (Bhakuni *et al*., 1969), insecticidal (Verma *et al*., 1982), anti-microbial (Sharma and Mehta, 1991), anti-filarial (Singhal *et al*., 1992; Nisha *et al*., 2007), anti-cancer (Arya *et al*., 2012a), anti-diabetic (Ani and Naidu, 2008; Fatima *et al*., 2010;

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Arya *et al*., 2012b), diuretic (Koti and Purnima, 2008), melanogenesis (Zhou *et al*., 2012) and wound healing activities (Sahoo *et al*., 2012). These properties will be discussed in details in the following sections to unravel the mystery and magical usage of *C. anthelminticum.*

CHEMICAL CONSTITUENTS OF *Centratherum anthelminticum*

C. anthelminticum has been investigated for its bioactive compounds since the early 1960. To date, more than 120 compounds were identified, ranging from fatty acid, sterols, sesquiterpene lactones, carbohydrates and flavonoids (Table 1). The chemical components were mostly identified from the seeds of *C. anthelminticum*, followed by leaves and aerial parts. Some of these identified compounds were isolated using chromatographic techniques and the structures were elucidated through spectroscopic techniques. A number of these compounds exhibited significant biological activities, which serve as the scientific evidence for the traditional usage of *C. anthelminticum*.

ANTHELMINTIC ACTIVITY

Traditional healers in India used seeds of *Centratherum anthelminticum* as a medication capable of causing the evacuation of parasitic intestinal worms and

Table 1: Bioactive compounds extracted from *C. anthelminticum*

Compounds	Parts	Isolated by
Flavonoids		
2',3,4,4',-tetrahydroxychalcone		
5,6,7,4´,-tetrahydroxyflavone		
7,3',4'-trihydroxydihydroflavone (Butin)	Seeds	Tian *et al*. (2004)
Kaempferol		
Quercetin glycoside		
Naringenin-7-*O* glucoside	Seeds	Arya *et al*. (2012c)
4H-1-Benzopyran-4-one,5-hydroxy-7- Methoxy-2-(3-methoxyphenyl)	Seeds	Arya *et al*. (2012a)
8, 5'-dimethoxy 3´, 4´-methylenedioxy 3,7-Dihydroxy flavone	Seeds	Yadav and Barsainya (1997)
Steroids		
Vernoanthelcin A		
Vernoanthelcin B		
Vernoanthelcin C		
Vernoanthelcin D		
Vernoanthelcin E		
Vernoanthelcin F		
Vernoanthelcin G		
Vernoanthelcin H		
Vernoanthelcin I		
Vernoantheloside A		
Vernoantheloside B	Seeds	Hua *et al*. (2012a)
Vernoanthelsterone A		
24ξ-hydroperoxy-24-vinyllathosterol		
(24R)-stigmast-7,22(E)-dien-3β-ol		
(22E,24R)-24-methyl-5α-cholesta-7,22-diene-3β,5,6β-triol		
(22E,24 S)-5α,8α-epidioxy-24-methyl-cholesta-6,22-dien- 3β-ol		
(22E,24S)-5α,8α-epidioxy-24-methyl-cholesta-6,9(11),22-trien-3β-ol	Seeds	Hua *et al*. (2012b)
(24α/R)-Stigmasta-7-en-3-one		
(24α/R)-Stigmasta-7, 9(11)-dien-3-one		
(24α/S)-Stigmasta-5, 22-dien-3β-ol		
(24α/S)-Stigmasta-7, 22-dien-3β-ol	Seeds	Mehta *et al*. (2005)
(Verma *et al*., 2004)		
(24ξ)-Stigmastanol		
Cholest-5-enol (cholesterol)		
(24α/R)-Ergost-5-enol (campesterol)		
(24β/S)-Ergost-5-enol (22-dihydrobrassicasterol)		
(24α/S)-Ergosta-5,22-dienol (crinosterol)		
(24β/R)-Ergosta-5,22-dienol (brassicasterol)		
Ergosta-5,24(24'-dienol(24-methylenecholesterol)		
(24α/R)-Stigmast-5-enol (sitosterol)		
(24α/S)-Stigmasta-5,22-dienol (stigmasterol)		
Stigmasta-5,24(24') Z-dienol (isofucosterol)		
(24α/R)-Ergost-7-enol		
(24β/S)-Ergost-7-enol (fungisterol)		
Ergosta-7,24(24')-dienol (episterol)		
(24α/R)-Stigmast-7-enol (schottenol)		
(24α/S)-Sigmasta-7,22-dienol (spinasterol)		

Table 1: Continue

Compounds	Parts	Isolated by
Stigmasta-7,24(24′)Z-dienol (avenasterol)		
Stigmasta-8,14,24(24′)Z-trienol (vernosterol)		
4α -Methylergosta-7,24(24′)-dienol (gramiserol)		
4α-Methylstigmata-7,24(24′)Z-dienol (citrostadienol)		
24-Methylstigmasta-8,14,24(24′)Z-trienol(4α-methylvernosterol)		
24-Methyl-31-norlanosta-8,24(24′)-dienol (obtusifoliol)		
24-Methyl-9β,19-cyclo-31-norlanost-24(24′)-dienol (cycloeucalenol)		
9β,l9-Cyclolanost-24-enol (cycloartenol)		
24-Methyl-9β,19-cyclolanost-24(24′)-enol(24-methylenecycloartanol)		
Tirucalla-7,24-dienol		
Urs-12-enol (β-amyrin)		
Olean-12-enol (β-amyrin)		
D-friedo-Olean-14-enol (taraxerol)		
Lup20(29)-enol (lupeol)		
Fern-9(11)-enol (fernenol)	Seeds	Akihisa *et al.* (1992)
Naphthalene derivatives		
Centratherumnaphthyl pentol		
Centratherumnaphthyl hexol	Seeds	Singh *et al.* (2012)
Drostanolone AC	Seeds	Arya *et al.* (2012a)
Phenolic acid		
Caffeic acid		
3-O-caffeoylquinic acid		
4-O-caffeoylquinic acid		
5-O-caffeoylquinic acid		
3,4-di-O-caffeoylisoquinic acid		
3, 4-di-O-caffeoylquinic acid	Seeds	Wang *et al.* (2012), Arya *et al.* (2012c)
Triterpenoid saponins		
3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranosyl]-23-hydroxyolean-12-en-28-oic acid3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl]-hederagenin	Seeds	Mehta *et al*, (2010)
3-O-[β-D-glucopyranosyl-(1→3)- α-L-rhamnopyranosyl-(1→2)- α-L-arabinopyranosyl]-28-O-[β-D-glucuronopyranosyl-(1→4)-α-L-rhamnopyranosyl-(-3)-β-D-glucopyranosyl]-hederagenin	Seeds	Mehta *et al.* (2004)
Aliphatic constituents		
Hexatetracontane-16-ol 6, 9-icosadiene Butyl 11-hydroxyoctadecanoate		
Hexyl 3-hydroxynonanoate Hexyl 9-hydroxyheptatriacontanoate		
Heptadecyl nonadecanoate	Seeds	Verma *et al.* (2004)
1,E-11,Z-13-Octadecatriene	Seeds	Arya *et al.* (2012a)
Fatty acids		
Vernolic acid		
Trivernolin		
1,3-divernolin		
Decanoic acid		
Dodecanamide		
Pentadecanoic acid,14-methyl-methyl ester		
Tetradecanamide		
Hexadecanoic acid, ethyl ester		
Octadecanoic acid, ethyl ester		
Ethyl vernolate		
1,3-divernolin		
1-vernolin	Seeds	Gunstone (1954), Krewson *et al.* (1962), Liu *et al.* (2012) Arya *et al.* (2012c)
Oleic acid		
Linoleic acid		
Palmic acid		
Stearic acid	Seeds	Singh and Kaul (1999)
Glyceryl diolein		
Glyceryl diricin		
Glyceryl ricinolpalmitein	Seeds	Singh *et al.* (2012)
12,13-dihydroxyoleic acid	Seeds	Looi *et al.* (2013)
Sesquiterpene lactone		
Vernodalol		
Vernodalidimers A		
Vernodalidimers B		
Vernodalin	Seeds	Asaka *et al.* (1977), Liu *et al.* (2010) Looi *et al.* (2013)

Table 1: Continue

Compounds	Parts	Isolated by
Carbohydrates		
D-lactose		
D-Raffinose		
L-Sorbose		
D-Arabinose		
L-Rhamnose		
D-Glucose		
Maltose		
D-Fructose		
D-Galactose	Seeds	Yadava and Barsainya (1996)
D-Allose		
D-Mannitol, 1-thiohexyl		
Arabino-hetitol,2,3 : 5,6-dianhydro-1,7-dideoxy-2,6-di-e-methyl	Seeds	Arya *et al.* (2012a)
Others		
Abscisic Acid	Leaves	Sanyal *et al.* (1970)
2-Pentanone-4-hydroxy-4-methyl		
2-Morpholinoethyl isothiocyanate		
3(2H)-Benzofuranone,2,6-dimethyl		
Adipic acid monoamide		
Ethyl 4-isothiocyanatobutyrate	Seeds	Arya *et al.* (2012a)

showed successful results in deworming small children and adults. The anthelmintic property, as displayed by the name of the plant itself, demonstrates its great potential in expelling different types of house worms. This activity of the plant is evident through some scientific evaluations by the previous researchers.

Singh *et al.* (1985) demonstrated *in vitro* anthelmintic activity on the alcoholic extract of *C. anthelminticum* seeds against *Fasciolopsis buski, Ascaris lumbricoides* and *Hymenolepis nana* worms. Next, Iqbal *et al.* (2006) demonstrated *in vitro* and *in vivo* anthelmintic activity of *C. anthelminticum* seeds in sheep naturally infected with gastrointestinal nematodes. Crude Methanolic Extract (CME) and Crude Aqueous Extract (CAE) of *C. anthelminticum* seeds were applied *in vitro* and CME indicated higher activity compared to CAE. However, CME exhibited no anthelmintic activity in the *in vivo* studies and maximum reduction in fecal egg counts per gram (EPG) was observed in the animals treated with CAE (73.9% at 3 g kg^{-1} body weight on day 5 post-treatment) followed by Crude Powder (CP), which indicated 55.6% reduction at 3 g kg^{-1} body weight on day 3 post-treatment.

ANTIFILARIAL ACTIVITY

Lymphatic Filariasis (LF), commonly known as elephantiasis, is a tropical disease caused by the nematode parasites *Brugia malayi*, *Brugia timori* and *Wuchereria bancrofti*. Recent surveys show that more than 1.3 billion people in 72 countries, mostly in South-East Asia, Africa and other tropical areas are at high risk of LF (WHO, 2012).

There are claims of antifilarial activity of this plant seeds, thus study by Singhal *et al.* (1992) demonstrated antifilarial activities of the aqueous and alcoholic extract of *C. anthelminticum* seeds on *Setaria cervi*. Nisha *et al.* (2007) showed *in vitro* macrofilaricidal activity of *C. anthelminticum* seeds against adult *S. digitata*, the cattle filarial worm.

Mehta *et al.* (2010) investigated the antifilarial activity of the aqueous and methanolic extracts of *C. anthelminticum*. Both extracts inhibited spontaneous motility of the whole worm and the nerve-muscle preparation of *S. cervi*. Only the methanolic extract was able to block the stimulatory response of acetylcholine. The two extracts caused significant death of microfilariae *in vitro*, with LC_{50} and LC_{90} values of 75 and 32.5 mg mL^{-1}, respectively. The isolated glycosides, 3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranosyl]-23-hydroxyolean-12-en-28-oic acid and 3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-glucopyranosyl-(1→3)-β-D- glucopyranosyl]-hederagenin from the methanol extract were also active *in vitro* against the *S. cervi*. However, the antifilarial activity of the two compounds was not efficient.

ANTI-OXIDANT ACTIVITY

Oxidative stress and anti-oxidants: Reactive oxygen species (ROS) are oxygen containing molecules, which are highly disruptive to cellular function. They constitute most of the important free radicals with indispensable roles in homeostasis and cell signaling (Halliwell, 2006). These chemically reactive molecules are natural byproducts of aerobic metabolic processes like

respiration. Drastic increase in ROS by environmental stress like heat or UV exposure, could damage proteins, DNA, lipids and cause oxidative stress. Some disorders have been shown to associate with oxidative stress, including diabetes, inflammation, cancer, neural degenerative disease, atherosclerosis, ageing and chronic airway inflammation in asthma (Smith *et al*., 1996; Finkel and Holbrook, 2000; Rosen *et al*., 2001; Neumann *et al*., 2003; Zhang *et al*., 2009).

Anti-oxidants are compounds that prevent damage to cell structures caused by chemical reactions involving free radicals. 1940's marked the beginning of using synthetic anti-oxidant, butylated hydroxyanisole (BHA) in food. Other synthetic anti-oxidants, like butylated hydroxytoluene (BHT) and tertiary butyl hydroquinone (TBHQ), were used to inhibit or reduce oxidative rancidity of foods (Fasseas *et al*., 2008). However, serious side effects of synthetic anti-oxidants, including their carcinogenic potential, led to a general desire to replace them with natural anti-oxidants (Grice, 1988; Namiki, 1990; Altmann *et al*., 1986; Van Esch, 1986; Jayaprakasha and Rao, 2000; Miller *et al*., 2000a, b; Paydar *et al*., 2013b).

***C. anthelminticum*, a potential source of natural anti-oxidants:** The anti-oxidant property of *C. anthelminticum* was first reported by Ani and Naidu (2011). The anti-oxidant activity of different extracts (aqueous-methanol-acetone, aqueous-methanol and aqueous extracts) of *C. anthelminticum* seeds was determined by 1,1-Diphenyl-2-picrylhydrazyl (DPPH$^{\bullet}$), ABTS$^{\bullet+}$ radical scavenging and phosphomolybdenum reducing assays. The extracts showed significant anti-oxidant activity against DPPH and ABTS radicals. Aqueous methanol acetone extract indicated the highest DPPH$^{\bullet}$ (IC_{50} 20.8±0.18 μg), ABTS$^{\bullet+}$ (IC_{50} 8.3 μg) scavenging activity and phosphomolybdenum reducing power (IC_{50} 0.31 μg). They found a remarkable correlation between anti-oxidant activity and the total phenol content of *C. anthelminticum*, indicating the phenolic compounds might be responsible for the anti-oxidant activity of the seeds.

Furthermore, liposome oxidation and oxidative DNA damage assays were performed using egg lecithin and bacterial genomic DNA, respectively, to determine the protective effects of the extracts from free radicals. The highest inhibitory effect on phospholipid peroxidation and comprehensive protection activity against DNA damage was obtained from aqueous methanol acetone extract. In particular, the phospholipid peroxidation activity was 41 times higher than the standard anti-oxidant α-tocopherol (Ani and Naidu, 2011). Therefore they conclude that aqueous methanol acetone extract is a potent anti-oxidant agent in preventing serious damages to DNA and other biomolecules of living cells (Halliwell, 1991).

Arya *et al*. (2012a) tested the anti-oxidant activity of the chloroform fraction of *C. anthelminticum* seeds using DPPH radical scavenging, oxygen radical absorbance capacity (ORAC) and ferric reducing/anti-oxidant power (FRAP) assays (Arya *et al*., 2012a). The fraction exhibited a high dose-dependent inhibition of DPPH activity (IC_{50} 22.56±1.4 μg mL^{-1}) and FRAP value (1048.3 μM), compared to the positive controls, ascorbic acid and BHT. The ORAC value of the fraction (992.34±45.12 μM) was comparable to quercetin (1018.00±34.82 μM) (Arya *et al*., 2012a).

Overall, these *in vitro* studies have clearly demonstrated the worthiness of *C. anthelminticum* seeds as an alternative natural source to substitute the synthetic anti-oxidants. However, *in vivo* study using animal model is lacking to confirm the anti-oxidant potential of the seeds for clinical application.

ANTI-INFLAMMATORY ACTIVITY

Inflammation is a common condition seen in many diseases of high prevalence worldwide, such as rheumatoid arthritis, type 2 diabetes mellitus and cardiovascular diseases (Mueller *et al*., 2010). Different cultures of population practiced the use of plants or plant-derived compounds to treat inflammatory related diseases or disorders (Mueller *et al*., 2010; Paydar *et al*., 2013a). Some species under the family of Asteraceae, for instance, *Vernonia cinerea*, had been reported by a few studies to possess anti-inflammatory activity (Iwalewa *et al*., 2003; Mazumder *et al*., 2003). There are several components in *C. anthelminticum* found to be similar in the species of *Vernonia cinerea* such as flavanoid, steroid and alkaloid, which prompted the investigation of anti-inflammation activity in *C. anthelminticum*. Ashok *et al*. (2010) examined the anti-inflammatory activity of *C. anthelminticum* seed using acute and subacute animal models of inflammation.

***C. anthelminticum* in acute phase of inflammation:** The process of inflammation is mediated by various components in different phases. Early stage of inflammation is mainly mediated by the release of histamine, serotonin and bradykinin, while prostaglandin

level will increase in later stage (Chaudhari *et al*., 2012; De Melo *et al*., 2006). Ashok *et al*. (2010) showed that both petroleum ether and alcohol extracts were effective on oedema reduction after 3 hours, with percentage inhibition of 46.15 and 41.54%, respectively, in carrageenan-induced oedema rats. The finding was comparable to the standard drug, sodium diclofenac (50.77%). The standard sodium diclofenac has been reported to inhibit prostaglandin synthethase (Ku *et al*., 1975), indicating that the extracts could have similar prostaglandin release inhibition activity. This hypothesis was also supported by Purnima *et al*. (2009), as they reported the anti-pyretic property of *C. anthelminticum* petroleum ether and alcohol extracts using brewer's yeast-induced fever model in rat. The effects of *C. anthelminticum* were similar to paracetamol in reducing fever induction caused by prostaglandin production in central nervous system (Moltz, 1993; Purnima *et al*., 2009). In the same study, the authors showed that both extracts demonstrated analgesic effect using Eddy's hot plate methods in mice compared to the standard drug, ibuprofen (Purnima *et al*., 2009).

Another possibility of anti-inflammatory activity of *C. anthelminticum* could be mediated by inhibiting myeloperoxide (MPO). MPO activity marks the accumulation of polymorphonuclear cells (PMNs) such as neutrophils, monocytes and macrophages in subplantar areas. The level of MPO correlates to the degree of inflammation (Krawisz *et al*., 1984). In Ashok's study, the petroleum ether and alcohol extracts of *C. anthelminticum* exhibited anti-inflammatory activity by MPO inhibition and reducing the infiltration of inflammatory cells (Ashok *et al*., 2010).

***C. anthelminticum* in subacute phase of inflammation:** Ashok *et al*. (2010) used the cotton pellet-induced granuloma test, a method employed to access the transudative, exudative and proliferative components of subacute inflammation (Swingle and Shiderman, 1972). The petroleum ether and alcohol extracts of *C. anthelminticum* at the dose of 100 mg kg^{-1} indicated significant inhibition of wet weight granuloma at 42.62 and 36.13%, respectively. To further prove the anti-inflammatory effect, they measured the alkaline phosphatase (ALP) level in the blood, as it acts as a marker for acute inflammation (Krotzsch *et al*., 2005). The petroleum ether and alcohol extracts showed 60.79 and 44.30% ALP inhibitory activity, respectively, at 200 mg kg^{-1} compared to standard drug, diclofenac (66.23%). Interestingly, this study showed that both extracts of *C. anthelminticum* and diclofenac exhibited similar anti-inflammatory effects. However, the animal models developed significant gastric lesion when they were administered with diclofenac, suggesting *C. anthelminticum* extracts can be a safer alternative for acute and subacute inflammation treatment (Ashok *et al*., 2010).

MELANOGENESIS ACTIVITY

Vitiligo, or commonly regarded as leucoderma, is a depigmentation disorder characterized by white patches on the skin. This condition is caused by default function of melanocytes (Kaur *et al*., 2012). Treating leucoderma with *C. anthelminticum*'s fruit extract is a popular practice among uygur ethnic minority in China. However, the mechanism of the extract on melanogenesis was unknown. Zhou *et al*. (2012) demonstrated that the ethanol extract of *C. anthelminticum* fruit was able to enhance the tyrosinase activity and melanin synthesis in cell-lines B16F10 (murine B16 melanoma cell line) and NHMC (normal human primary melanocytes) after 48 h treatment, indicating that *C. anthelminticum* fruit extract could treat leucoderma by enhancing melanogenesis. Tian *et al*. (2004) separated and identified three effective flavonoids from *C. anthelminticum* seeds for vitiligo, including 2',3,4,4',-tetrahydroxychalcone, 5,6,7,4',-tetrahydroxyflavone and Butin.

The microphthalmia-associated transcription factor (MITF) is crucial in expressing pigmentation-related genes and proliferating melanoma cells (Vachtenheim and Borovansky, 2012), whereas tyrosinase protein is needed to synthesise melanin pigment (Hara *et al*., 1994). The protein level of MITF and tyrosinase were up-regulated after the skin cells were treated with *C. anthelminticum* extract (Zhou *et al*., 2012). This effect is reported to be induced via the activation of p38 mitogen activated protein kinase (MAPK) and cyclic adenosine monophosphate response element-binding (CREB) (Saha *et al*., 2006; Singh *et al*., 2005). Addition of p38 MAPK and protein kinase A (PKA) inhibitors abrogated the up-regulation of MITF and tyrosinase. Of note, melanin synthesis was suppressed by p38 MAPK inhibitor but not by PKA inhibitor (CREB activation mediator). This result indicated that *C. anthelminticum*-induced melanogenesis was primarily mediated through p38 MAPK activation and secondarily by CREB activation (Zhou *et al*., 2012).

ANTI-DIABETIC ACTIVITY

Diabetes mellitus is a metabolic disorder characterized by chronically high blood glucose level. It can be

classified into two major categories: Type 1 (caused by destruction of beta cells of islet of Langerhans, resulting in insulin deficiency) and Type 2 (caused by disorder in insulin secretion or action, resulting in predominantly insulin resistance) (Alberti and Zimmet, 1998). Based on a study by King *et al.* (1998), there will be an increase prevalence of diabetes in world population, in which developing countries such as India shows the highest rise estimated at 59%. Thus, there is a need for cheaper and more effective treatment. Due to the limitation on available resources and reported side effects of modern drugs, many researchers have turned their attention to medicinal plants in hope to find a possible cure (Grover *et al.*, 2002; Modak *et al.*, 2007).

Activity of *C. anthelminticum* on α-glucosidase, α-amylase and PTP-1B: In a report by Ani and Naidu (2008), the anti-hyperglycemic effect of *C. anthelminticum* was evaluated against key enzymes important for glucogenesis. Different concentrations of aqueous methanol-acetone extract were tested on the activity of α-glucosidase (PNP-G hydrolysis, sucrose and maltase). The IC_{50} values for the *C. anthelminticum* extract on disaccharide substrates PNP-G, sucrose and maltose were 500.5, 34.1 and 62.2 μg, respectively. This results show that *C. anthelminticum* extract is a potent sucrase and maltase inhibition agent compared to PNP-G hydrolysis. In contrast, the synthetic drug, acarbose showed high affinity towards sucrase only. This data indicates that *C. anthelminticum* will be a better alternative for diabetic treatment because it reduces hydrolysis of the disaccharides via sucrase and maltase inhibition, resulting in lower blood glucose level. They further validated the findings by administrating maltose and different dosages of extract orally into rats. These investigations proved the potentiality of *C. anthelminticum* in suppressing maltose digestion and absorption (Ani and Naidu, 2008).

In contrast, the results of human salivary α-amylase test showed less inhibition by the extract compared to standard, acarbose, with IC_{50} values of 185.5 and 17.4 μg, respectively (Ani and Naidu, 2008). Although *C. anthelminticum* showed lower inhibitory effect on α-amylase, a report by Krentz and Bailey (2005) indicates that lower inhibitory effect on α-amylase and higher inhibitory effect on α-glucosidase will be a better formulation for management of type 2 diabetes condition. This is important as α-amylase catalyzes the digestion of dietary starch to disaccharides and trisaccharides, which act as a source of glucose to the human body.

Protein Tyrosine Phosphatase-1B (PTP-1B) is an intracellular phosphatase, which negatively regulates the insulin signaling pathway. PTP-1B-deficient mice have significantly reduced body weight and lower adiposity despite being given high fat diet compared to the wild-type control (Tsou *et al.*, 2012). In view of these protective effects, PTP-1B has emerged as a new target in tackling diabetes and other associated metabolic syndromes. Recently, we found that the methanolic fraction of *C. anthelminticum* seeds inhibited PTP-1B enzyme at IC_{50} 38±5.8 μM, compared to standard drug, RK-682 (4.1±0.6 μM). In contrast, *C. anthelminticum* leaves were less effective (64±5.8 μM), possibly due to lower total flavanoid, phenolic, tannin content in the leaves (Arya *et al.*, 2013).

Activity of *C. anthelminticum* in pancreatic cell-line and diabetic animal model: Bhatia *et al.* (2008a) showed that water extract of *C. anthelminticum* seeds at dosages of 200 and 500 mg kg^{-1} markedly reduced blood glucose level after 7-day treatment, at 35.61 and 40.1%, respectively. Meanwhile, the standard drug, glibenclamide, showed a decrease at 48.63%. Diabetic rats treated with *C. anthelminticum* extracts exhibited less complications such as thirst, tiredness and irritation, compared to rats treated with glibenclamide. Shah *et al.* (2008) reported similar observations using methanol extract of *C. anthelminticum.* These studies indicated that treatment with *C. anthelminticum* is beneficial with less side effects, compared to the standard drug glibenclamide (Bhatia *et al.*, 2008b; Shah *et al.*, 2008).

In 2012, our group reported the anti-diabetic potential of the crude methanolic fraction of *C. anthelminticum* seeds (CAMFs) using β-TC6 mouse pancreatic cell-line and type 2 diabetic rat model. CAMFs showed non-cytotoxic effect on β-TC6 cell proliferation at 50 mg mL^{-1}, compared to untreated control cells. Glucose uptake was increased via up-regulation of glucose transporter proteins, Glut-2 and Glut-4 expression level in CAMFs treated cells. *In vivo* studies on streptozotocin induced diabetic rat models revealed that CAMFs significantly reduced hyperglycemia by augmenting insulin secretion in type 2 diabetic rats (Arya *et al.*, 2012b). Thus, we hypothesize that CAMFs carried out anti-diabetic actions by increasing glucose uptake and insulin secretion (Fig. 1).

In addition, further studies result indicated the power of CAMFs by decreasing type 2 diabetes and its associated complications by increasing serum insulin, C-peptide, total protein and albumin levels, significantly, whereas, elevated blood glucose, glycated hemoglobin, lipids and enzyme activities were restored to near normal. CAMFs confirmed antioxidant potential by

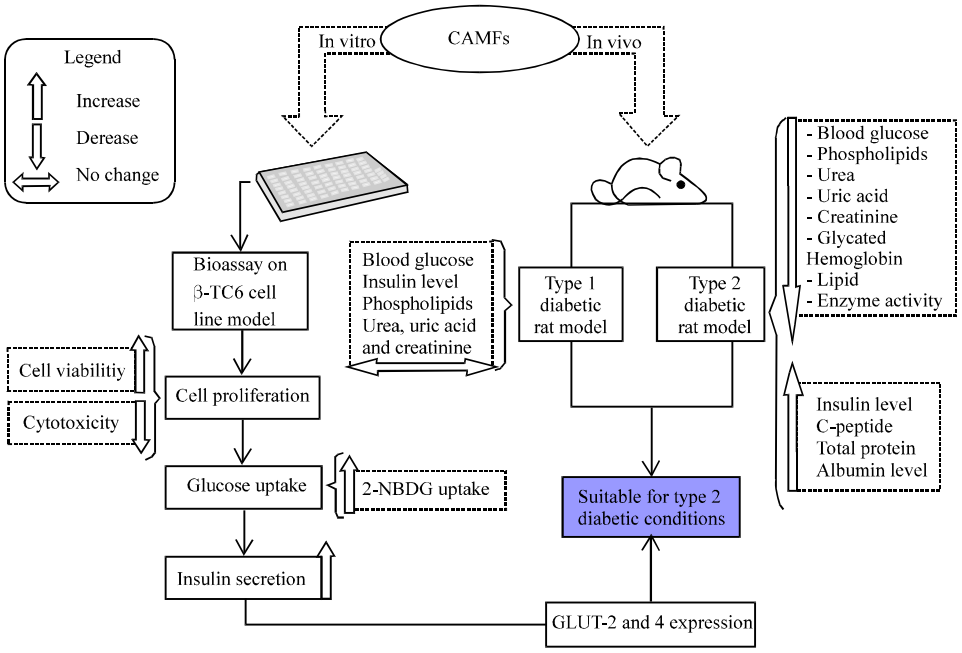

Fig. 1: Graphical image depicting the anti-diabetic mechanism of crude methanolic fraction of *C. anthelminticum* (modified from Arya *et al*., 2012b, c)

elevating glutathione (GSH) and reducing malondialdehyde (MDA) levels in diabetic rats. Interestingly, CAMFs down-regulated elevated tumor necrosis factor α (TNF-α), interleukin (IL)-1β and IL-6 in the tissues and serum of the diabetic rats. This study postulated that CAMFs may be a valuable candidate nutraceutical for insulin-resistant type 2 diabetes and its associated complications such as dyslipidemia, oxidative stress and inflammation (Fig. 1) (Arya *et al*., 2012c).

WOUND HEALING ACTIVITY

Wound healing is a dynamic and intricate process of skin (or any organ-tissue) self-repairing by restoring cellular structures and tissue layers (Nguyen *et al*., 2009). A vital component in wound healing is angiogenesis, which is the formation of new blood vessels from the pro-existing vessels. Various medicinal plants have been used in treating wounds and promoting angiogenesis (Nagori and Solanki, 2011; Majewska and Gendaszewska-Darmach, 2011). Sahoo *et al*. (2012) studied the wound healing property of *C. anthelminticum* seeds on excision and incision wounds in Wistar albino rats. The aqueous methanol extract of *C. anthelminticum* seeds was prepared in ointment form with two concentrations, 5% w/w and 10% w/w. The results showed that 10% (w/w) *C. anthelminticum* ointment and standard drug, nitrofurazone ointment exhibited complete healing of the wound on the 18th day, with wound area of 00±0.4 mm^2 and 00±0.0 mm^2, respectively. Whereas lower healing activity was observed with 5% (w/w) *C. anthelminticum* ointment application.

Histological study on the skin specimens collected from the healed wounds showed that the wounds either treated with the *C. anthelminticum* extract and the standard drug exhibited less scar formation and more healing characteristics (e.g., angiogenesis, formation of epithelial and keratin tissues). The results obtained from this study revealed the potential of *C. anthelminticum* as a wound healing therapeutic agent. However, the chemical components of *C. anthelminticum* which contribute to this wound healing mechanisms are yet to be investigated (Sahoo *et al*., 2012).

ANTI-MICROBIAL ACTIVITY

The antimicrobial potential of different extracts of *C. anthelminticum* seeds was first investigated by Sharma and Mehta (1991), using filter paper disc method. They reported significant inhibitory effects of the extracts against several bacteria and fungi. Later, other studies on the antimicrobial activity of various extracts of *C. anthelminticum* indicated that it could serve as a potential antimicrobial agent against a number of pathogenic bacterial and fungal strains.

Anti-*bacillus* spp., Activity: *Bacillus subtilis* and *Bacillus cereus* of Bacillaceae family are Gram-positive heterotrophic rod-shaped bacteria with the ability to produce protective endospores. *B. subtilis* is usually found in water, soil, air and decomposing matter (Alexander, 1977). It produces an extracellular toxin known as subtilisin, which is capable of causing allergic reactions (Edberg, 1991), despite its low toxigenic property (Gill, 1982). *B. cereus* is the cause of fried rice syndrome (Glenn *et al*., 2005) that may lead to severe nausea, vomiting and diarrhea (Kotiranta *et al*., 2000). Ani (2008) reported that aqueous methanol acetone extract of *C. anthelminticum* showed high inhibitory activity against *B. subtilis* and *B. cereus*. The extract has minimum inhibitory concentration (MIC) at 50±7 μg mL^{-1} against *B. cereus* (Ani, 2008). However, Patel *et al*. (2012) reported that ethanol extract of *C. anthelminticum* showed low inhibitory activity against B. *cereus* and B. *pumilus*, with MIC at 10 mg mL^{-1}. Hua *et al*. (2012a) isolated and identified 24 μ-hydroperoxy-24-vinyllathosterol, from the seed of *C. anthelminticum*. The compound showed high activity on *B. cereus* and *B. subtilis* with MIC values of 7.25 and 15.5 μg mL^{-1}, respectively.

Anti-Enterobacteriaceae activity: The Enterobacteriaceae is a large family of gram-negative rod-shaped bacteria that comprises of many harmless symbionts and familiar pathogens. Mehta *et al*. (2005) reported two new steroidal compounds, (24α/R)-Stigmasta-7-en-3-one and (24α/R)-Stigmasta-7, 9(11)-dien-3-one, from benzene:acetone extract of *C. anthelminticum* seeds. These compounds possessed moderate activity (inhibition zone of 9-16 mm) against some bacterial species of Enterobacteriaceae family, including *Salmonella typhimurium*, *Escherichia coli* and *Proteus vulgaris*. Patel *et al*. (2012) also reported anti-microbial activity against Enterobacteriaceae family. The ethanol extract of *C. anthelminticum* seeds showed moderate activity against *Klebsiella pneumonia* (inhibition zone of 10-15 mm) and low activity against P. *vulgaris*, *E. coli* and S. *typhi* (inhibition zone of 1-9 mm).

Anti-*Staphylococcus aureus* activity: *Staphylococcus aureus*, a Gram-positive spherical bacterium of Staphylococcaceae family, is frequently found in the human respiratory tract and skin surface. *S. aureus* is one of the main pathogenic causes of skin and tissue infections, pneumonia, septicemia and device-associated infections (Harmsen *et al*., 2003). Ani reported high antibacterial activity of aqueous methanol acetone extract of *C. anthelminticum* against *S. aureus* with MIC of 260±18 μg mL^{-1} (Ani, 2008).

Another study has also reported the antimicrobial activity of methanolic and acetone extracts of *C. anthelminticum* seeds on *S. aureus* using agar diffusion technique (Mehta *et al*., 2010). The methanol and acetone extracts possessed very good (12.0-14.0 mm) and moderate (9.0-11.0 mm) activity, respectively, against *S. aureus*. Two novel triterpenoid saponins, 3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranosyl]-23-hydroxyolean-12-en-28-oic acid and 3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl]-hederagenin have been isolated from the seeds. Both compounds showed high to moderate activity against *S. aureus*. Recently, 24ξ-hydroperoxy-24-vinyllathosterol, a steroidal compound, has been isolated from C. *anthelminticum* seeds. The compound exhibited high activity on *S. aureus* with MIC value of 3.15 μg mL^{-1} (Hua *et al*., 2012b).

Anti-*Pseudomonas aeruginosa* activity: *Pseudomonas aeruginosa* is a genus of gram-negative rod-shaped bacteria that belongs to the family Pseudomonadaceae (Rossolini and Mantengoli, 2005). It is reported as one of the most common causes of nosocomial infections and a typical opportunistic pathogen. The intrinsic resistance of *P. aeruginosa* to various antimicrobial agents has made it difficult to be eliminated (Rossolini and Mantengoli, 2005). Patel *et al*. (2012) showed that ethanol extract of *C. anthelminticum* seeds is effective against *P. aeruginosa*, with MIC of 2 mg mL^{-1}.

Activity on other bacterial species: Mehta *et al*. (2005) isolated and identified four steroidal compounds (Table 1) from the seeds of *C. anthelminticum*. The compounds were tested for their antibacterial activity against various bacterial species using agar diffusion technique. Among the compounds (24α/R)-Stigmasta-7-en-3-one exhibited moderate antibacterial activity (disc diameter, 9.0-16.0 mm) on *Salmonella typhimurium* and *Escherichia coli*, while (24α/R)-Stigmasta-7, 9(11)-dien-3-one showed moderate activity on *Proteus vulgaris*. Further more, six steroidal compounds have been isolated from the seeds of *C. anthelminticum* (Table 1) and tested for their antibacterial activity against *E. coli*

(Hua *et al*., 2012b). Only 24 μ-hydroperoxy-24-vinyllathosterol showed high activity on E. coli with MIC value of 7.25 μg mL^{-1}.

Mehta *et al*. (2010) also reported the antimicrobial activity of methanolic and acetone extracts of the seeds of *C. anthelminticum* against various bacteria using agar diffusion technique. The methanol extract possessed a significant activity against *Arthrobacter* (16.0-20.0 mm), a very good activity against *Micrococcus luteus* (12.0-14.0 mm) and moderate activity against *Klebsiella pneumonia* (9.0-11.0 mm). The acetone extract showed strong activity against *Arthrobacter* (12.0-14.0 mm) and moderate activity against *M. luteus*. However, it showed poor activity against *E. coli* and *K. pneumonia* (6.8-8.0 mm).

Anti-fungal activity: Singh *et al*. (2012) reported the antifungal activity of *C. anthelminticum* seed extracts on *Aspergillus flavus*, *Candida albicans* and *Penicillium citrinum*. This activity was demonstrated by methanolic extract of the seeds of *C. anthelminticum* and two of the isolated compounds, centratherumnaphthyl pentol and centratherumnaphthyl hexol. The extract and the compounds exhibited inhibitory effect on all fungal strains tested. Poor antifungal activity was also reported from (24α/R)-stigmasta-7-en-3-one and (24α/R)-stigmasta-7, 9(11)-dien-3-one, steroidal compounds isolated from the seeds of *C. anthelminticum,* against *Aspergillus niger, A. alternate* and *A. flavus* (Mehta *et al*., 2005).

The methanol and acetone extracts of *C. anthelminticum* seeds have been also investigated for their antifungal activity against various fungi. The methanol extract showed very good to moderate activity against *Trichothecium roseum* (12.0-14.0 mm), *Candida albicans* (9.0-11.0 mm) and *Fusarium solani* (12.0-14.0 mm), while no activity was observed against *Penicillium notatum*. Meanwhile, the acetone extract showed lower activity against the fungi than the methanol. Two new triterpenoid saponin compounds, 3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[α-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranosyl]-23-hydroxyolean-12-en-28-oic acid and 3-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-O-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl]-hederagenin, were isolated from the methanol extract of *C. anthelminticum* seeds. The compounds showed very good to moderate activity against *T. roseum*, *C. albicans*, *F. solani* and *P. notatum* (Mehta *et al*., 2010).

Overall, these studies imply the potential of *C. anthelminticum* seed extracts worth to be further developed as an alternative anti-microbial agent.

LARVICIDAL ACTIVITY

Srivastava *et al*. (2008) investigated the larvicidal activity of the petroleum ether extracts of *C. anthelminticum* against *Anopheles stephensi,* the primary mosquito vector of malaria. They reported significant larvicidal activity of both leaf and fruit extracts against instar larvae. The lethal concentration that caused 50% death of the larvae (LC_{50}) was 522.94 ppm and 162.60 ppm, respectively after 24 hours. The fruit extract exhibited higher toxicity compared with the leaf extract at both LC_{90} and LC_{50} levels. The findings indicated that the petroleum ether extract of *C. anthelminticum* fruits can serve as an active agent to control Anopheles larvae.

ANTI-TUMOR PROPERTY

Two novel elemanolide dimers, vernodalidimers A and B, were isolated from the seeds of *C. anthelminticum* and examined for their cytotoxic activity against Human promyelocytic leukemia cells (HL-60). Both compounds exhibited potent cell growth inhibitory effect on HL-60 cells with IC_{50} values of 0.72 and 0.47 μM, respectively (Liu *et al*., 2010).

In 2012, our group demonstrated that the chloroform fraction of *C. anthelminticum* (CACF) possessed higher anti-cancer activity compared to methanolic and hexane fractions (Arya *et al*., 2012a). CACF effectively inhibited growth of A549 (lung), PC-3 (prostate), MCF-7 (breast) cancer cells with IC_{50} values of 31.42±5.4, 22.61±1.7 and 8.1±0.9 μg mL^{-1}, respectively. In addition, we showed that CACF was less toxic to normal hepatic cells WRL-68 (54.93±8.3 μg mL^{-1}). We found that CACF dose-dependently inhibited the activation and nuclear translocation of NF-κB in TNF-stimulated MCF-7 cells (Arya *et al*., 2012a). This study revealed the potential of CACF in the treatment of breast cancer associated with oxidative stress conditions and inflammatory responses. Recently, we successfully isolated and identified two compounds from CACF through bioassay guided isolation, vernodalin and 12,13-dihydroxyoleic acid (Looi *et al*., 2013). Vernodalin, a sesquiterpene lactone, exhibited potent growth inhibition on MCF-7 and MDA-MB-231, human breast cancer cells, with IC_{50} values of 2.5±0.3 and 3.4±0.6 μg mL^{-1}, respectively. Meanwhile,

12,13-dihydroxyoleic acid indicated no activity on the tested cell lines. Morphological studies of vernodalin-treated samples suggested cell death by apoptosis, as evidenced by cell shrinkage, nuclear condensation and formation of apoptotic bodies (Looi *et al*., 2013). *In vivo* studies (toxicology and mouse xenograft model) are undergoing to further understand the mechanism of vernodalin isolated from *C. anthelminticum*.

DIURETIC ACTIVITY

Diuretics are therapeutic agents that can adjust the composition and volume of body fluids by increasing the rate of urine flow and sodium excretion. They are used in treating a number of diseases including nephritic syndrome, cirrhosis, congestive heart failure, renal failure, pregnancy toxaemia and hypertension (Agunu *et al*., 2005). Most of the diuretic drugs indicate high efficiency in sodium excretion. However, they cause a drop in blood potassium levels which eventually leads to high blood pressure and may induce the risk of developing type 2 diabetes (Shafi *et al*., 2008; Grossman *et al*., 2011). Thus, investigators are hoping to find new efficient diuretic drugs with less side effects (Rang *et al*., 1994).

Koti and Purnima (2008) tested petroleum ether, chloroform and alcohol extracts of *C. anthelminticum* seeds on Albino Wistar rats, at dosage of 200 mg kg^{-1} body weight. The alcohol and chloroform extracts exhibited significant diuretic activity, compared to the standard drug, spiranolactone. Both extracts significantly increased Na^+ excretion and surprisingly, decreased K^+ excretion, drastically. This finding indicated the potential of *C. anthelminticum* as a new source of potassium-sparing diuretic.

ANTI-VIRAL ACTIVITY

So far, only one report on the anti-viral activity of *C. anthelminticum* is available in the literature. Bhakuni *et al*. (1969) reported the anti-viral effect of *C. anthelminticum* extracts against Ranikhet (Newcastle) disease virus and Vaccinia virus. Hence, further investigations are required to confirm and clarify the possible mechanisms of antiviral activities of the plant.

INHIBITION OF AROMATASE

Aromatase is an enzyme responsible for the conversion of the adrenal androgen substrate androstenedione, to estrogen in peripheral tissues (Evans *et al*., 1986). Estrogen participates also in pathological processes such as breast, endometrial and ovarian cancers (Stocco, 2008). Thus, aromatase inhibitors are important in inhibiting the peripheral production of estrogen, eliminating the external supply of estrogen to the tumour cell (Bhatnagar *et al*., 2001). In searching for novel compounds that can promote estrogen biosynthesis, Hua *et al*. (2012b) isolated six steroidal compounds from *C. anthelminticum* seeds and tested them for their effects on estrogen biosynthesis in human ovarian granulosa-like KGN cells. Among the compounds (Table 1), only 24μ-hydroperoxy-24-vinyllathosterol was effective as it increased the 17β-estradiol biosynthesis with EC_{50} value of 56.95 μg mL^{-1}.

FUTURE PROSPECT

Several investigators reported significant medicinal potential of different extracts of *C. anthelminticum* and their wide therapeutic activities against numerous illnesses. These evidential properties indicate the importance of this plant for further studies directed to drug development. However, most of the studies were conducted with extracts and there is a lack in isolation of bioactive compounds as well as mechanistic studies. Recent studies unraveled the anti-cancer activity of *C. anthelminticum* extract, which revealed another aspect of its potential to be investigated in future studies. Likewise, anti-viral, larvicidal and wound healing activities could be further explored. Advanced molecular approaches, such as molecular docking studies can contribute towards plant-based drug development in the future.

CONCLUSION

Numerous scientific investigations have indicated high medicinal potential of *C. anthelminticum* in many diseases (Fig. 2). Despite these facts, clinical trials using extracts or bioactive compounds are absent, possibly due to mass production issues or lack of mechanistic studies to understand its pharmacological effects. Thus, there is a definite requirement for further studies, both clinical and on the bench for further development of extracts or bioactive compounds isolated from *C. anthelminticum*. Improvement of medicinal chemistry methods could provide the opportunity to further evaluate the natural compounds and to investigate their biosynthetic pathways.

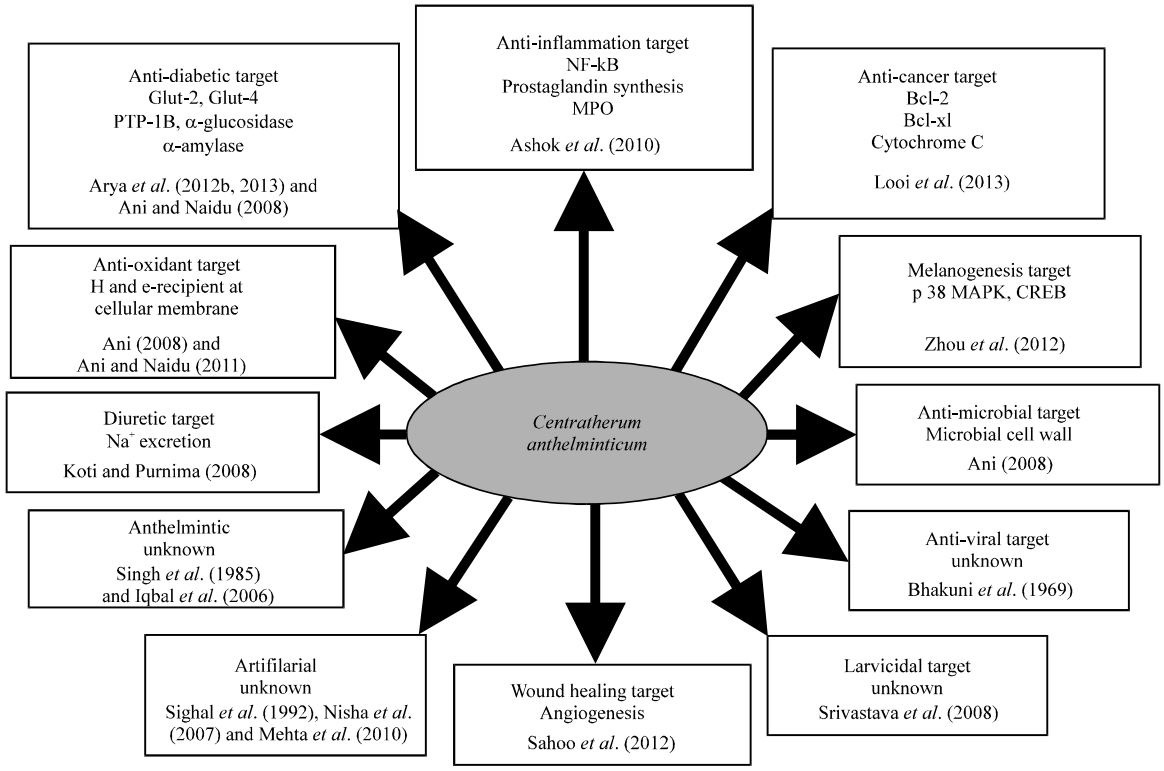

Fig. 2: Overview of various biological effects and the involvement of multiple signaling pathways targeted by *C. anthelminticum*

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