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The Chemical Constituents and Pharmacology of *Centratherum anthelminticum*

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Abstract: Centratherum *anthelminticum* commonly known as 'black cumin', a traditional Ayurvedic medicine, has been used for centuries for curing common ailments such as fever, cough, and diarrhoea, and its is also used as a general tonic. A wide range of secondary metabolites such as: aliphatic fatty acids, flavones, saponins, steroids and glycosides have been reported from the C. *anthelminticum*. Its extracts are reported to possess a wide range of pharmacological activities such as: analgesic, antibacterial, antifungal, antidiuretic, antifilarial, antihelmintic, antihyperglycemic, antimicrobial, antimalarial and antipyretic properties. This review is an effort to summarize the chemical constituents, pharmacological properties of C. *anthelminticum*.
Keywords: *Centratherum anthelminticum*, Chemical Constituents & Pharmacology of *Centratherum anthelminticum.*

Introduction

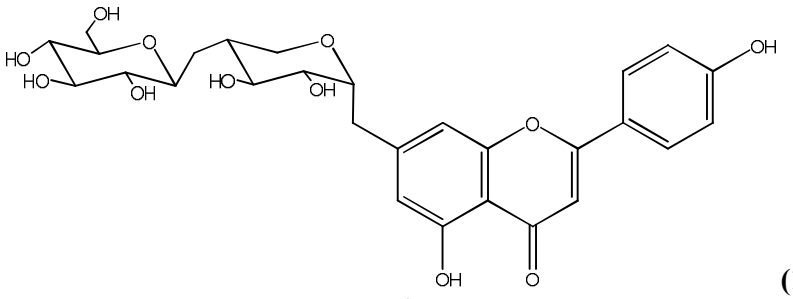
Centratherum anthelminticum (Willd.) Kuntz belongs to the family compositae. It is is widely useed as a preparation in the Ayurvedic system of medicine preparations and is distributed widely in India, even to the heights of 5500 ft. Certain other plants such as *Nigella sativa* and *Bunium persicum* Boiss are also known as kalajiri or black cumin in India, but even than these three species are still called black cumin or kalajiri [1-3].

C. anthelminticum is very important in traditional medicine for the treatment of fever, cough, and diarrhoea, and as a general tonic. It is also known to exhibit antiasthmatic, alterative, antiphlegmatic, cardiac, diuretic, digestive and febrifugal properties, and is known to be effective in kidney disorders [4-9].

Isolation and chemical investigation

The earliest investigations began when Jaiswal *et al.*, estimated the contents of albumins, globulins, and glutelins and certain other free amino acids in eight medicinal plants including *C. anthelminticum* for estimating the food value of these plants. *C. anthelminticum* did not show any promising results as sources of food proteins [10-11].

Yadava and Barsainya, reported two novel compounds a flavone glycoside **(1)** and 8,5'-dimethoxy 3',4'-methylenedioxy 3,7-dihydroxy flavone **(2)** from the seeds *C. anthelminticum* [8, 7, 12].



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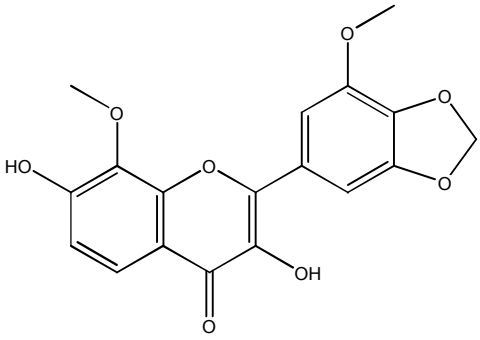

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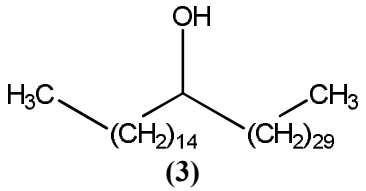
The chemical examination of the oil and seed meal of *C. anthelminticum* showed that the oil is greenish and semi viscous with a specific gravity of 0.945 and is insoluble in 70% alcohol. The major component of the oil was found to be vernolic acid 70.28%, followed by linoleic 15.84%, oleic 5.65% and palmitic 2.30% and stearic acids 0.42%. The defatted seed meal were found to contain 5.2% ash and 28.4% protein [13].

Verma *et al.*, identified from the seeds of *C. anthelminticum* six new compounds hexatetracontan-16-ol **(3)**, 6,9-eicosadiene **(4)**, Butyl 11-hydroxy octadecanoate **(5)**, hexyl 3-hydroxynonanoate **(6)**, hexyl 9-hydroxyheptatriacontanoate **(7)** and heptadecyl nonadecanoate **(8)**, along with the known stigmasterol [14].



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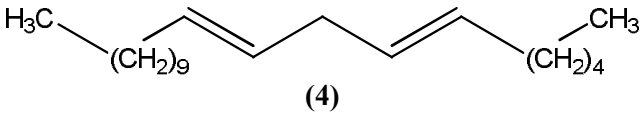

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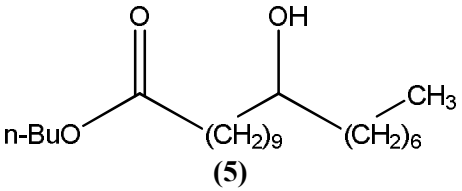

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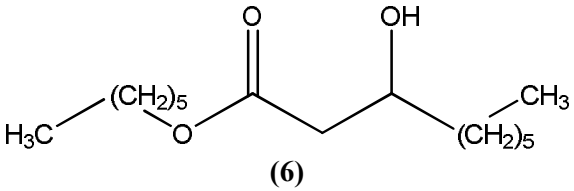

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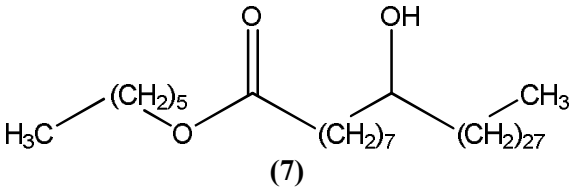

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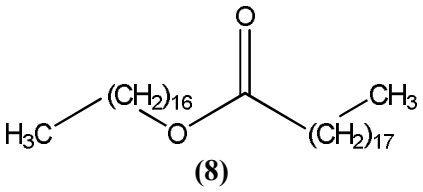

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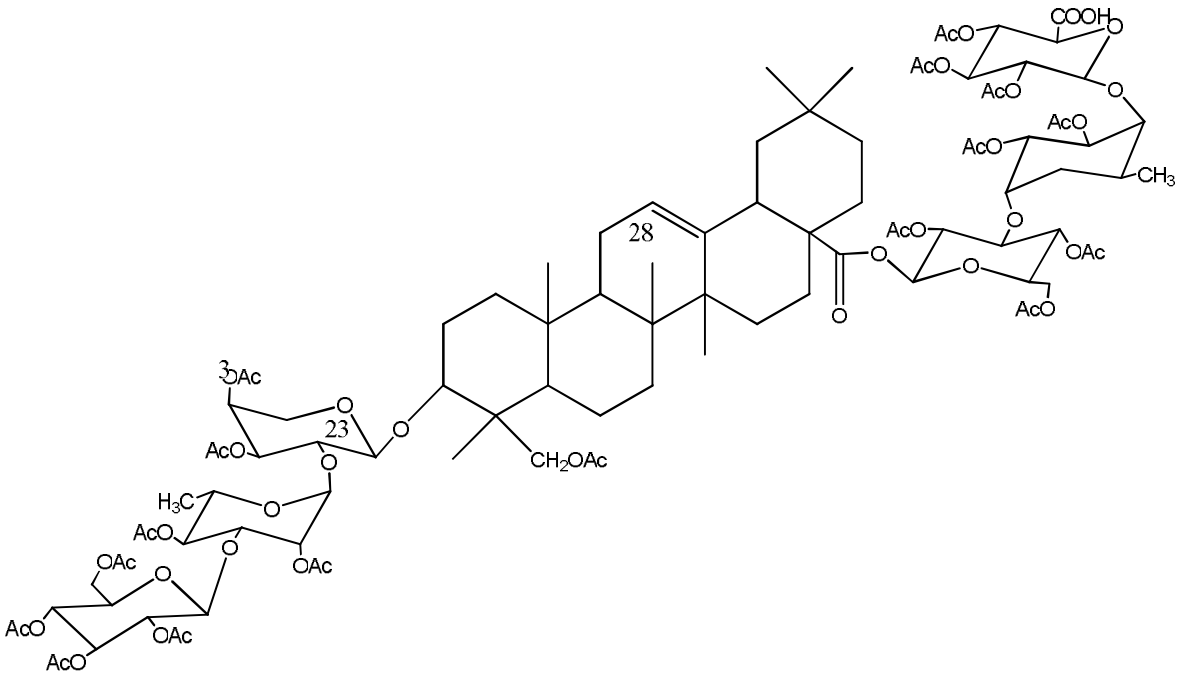

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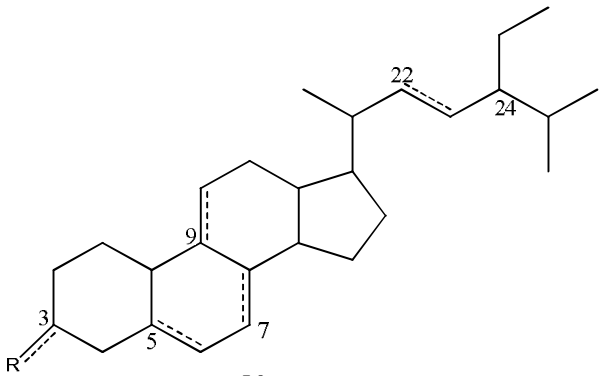
Mehta *et al.*, reported from the seeds of *C. anthelminticum* a novel saponin 3-*O*-[β-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl]-28-*O*-[β-D-glucuronopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranosyl]-hederagenin **(9)** [15].

Isolation with bioactivity

Batra *et al.*, exaimned the seed oil of *C. anthelminticum* was found to exhibit palmitic 30.4%, stearic 11.9%, oleic 23.7%, and linoleic acid 19.9%, and the oil was found to be active against several bacteria and fungi [16].

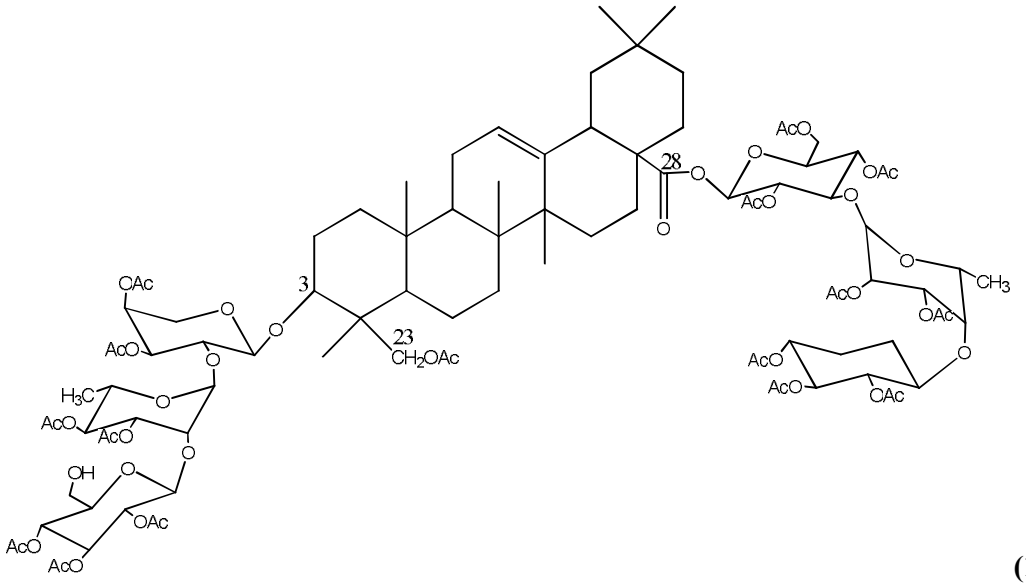
Mehta *et al.*, reported two new compounds (24α/R)-Stigmasta-7-en-3-one **(10)**, (24α/R)-Stigmasta-7, 9(11)-dien-3-one **(11)** from the benzene: acetone extract of the seeds of *C. anthelminticum*, and two known compounds from the (24α/S)-Stigmasta-5, 22-dien-3β-ol and (24α/S)-Stigmasta-7, 22-dien-3β-ol from the ethanol extract of the seeds of *C. anthelminticum*. The new compounds **(10)** and **(11)** were examined for antimicrobial activity against several human pathogenic bacteria and fungi, by agar diffusion technique, and the compounds were found to be moderately active against certain bacteria and fungi [4].



10.R = O, Δ^{7-8} (24α/R)
11.R = O, $\Delta^{7-8, 9-11}$ (24α/R)

Mehta *et al.*, reported from the methanolic extract of the seeds of *C. anthelminticum* two novel acetylated 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 **(12)** 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]-23-hydroxyolean-12-en-28-oic acid **(13)**. The methanol, acetone and aqueous extracts along with the purified compounds were also tested for antifilarial and antimicrobial activities. The methanol, acetone extracts and the purified compounds showed moderate to good activity against most of the bacteria and fungi.

The aqueous and methanolic extract caused inhibition of spontaneous motility of the whole worm and the nerve-muscle preparation of *Setaria. cervi*, characterised by reduced tone, amplitude and rate of contractions. The concentration required to inhibit the movements of the nerve-muscle preparation for aqueous and alcoholic extracts were l/25 and l/125, respectively. Only the methanol extract was found to block the stimulatory response of acetylcholine. Both the methanolic as well as the aqueous extracts caused death of microfilariae *in vitro*, LC_{50} and LC_{90} being 75 and 32.5 mg/mL, respectively. The purified compounds **(12)** and **(13)** were found to be active against *S. cervi*, but did not show any comparable antifilarial efficacy [5]. Later the trisaccharide units of these compounds were also synthesized [17, 2].



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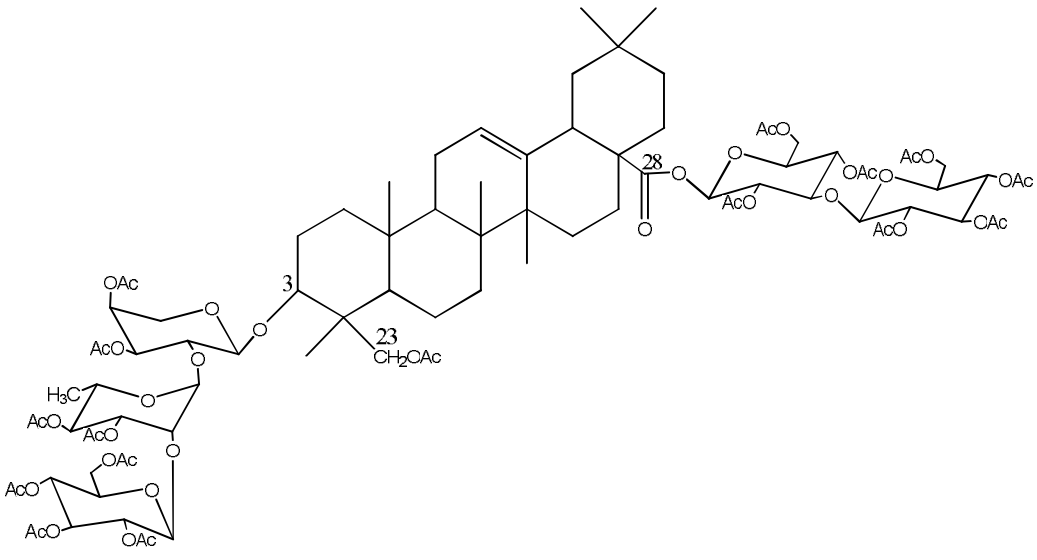

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Biological activities

Analgesic and antipyretic activities

Purnima *et al.*, examined the petroleum ether and alcohol extracts of the seeds of *C. anthelminticum* for analgesic and antipyretic activities, using brewer's yeast-induced fever model in rats, acetic acid-induced writhing and Eddy's hot plate methods in mice. The petroleum ether and alcohol extracts indicated significant reduction in the number of writhes in acetic acid-induced writhing and increase in the paw licking time to heat stimuli in the hot plate method. Highest analgesic activity was observed at 90 minutes time after the administration of the extracts as compared to the control, and both the extracts inhibited elevated body temperature when compared to corresponding control. Thus the study suggested that both the *C. anthelminticum* extracts exhibit analgesic and antipyretic activities [18].

Antifilarial activity

Singhal *et al.*, 1992), examined the seed extracts of *C. anthelminticum* on the spontaneous movements of the whole worm and nerve-muscle preparation of *S. cervi*. The extracts (ethyl acetate, acetone, methanol and water) showed similar effect, of causing inhibition of spontaneous motility of the nerve-muscle preparation of *S. cervi* characterized by decreased amplitude and frequency of contractions, and the inhibitory activity was found to be reversible. The extracts did not block the cholinergic receptors as evidenced by the presence of unaltered stimulant response of acetylcholine in the presence of drug in bathing fluid [19].

Antihelmintic activity

Devi *et al.*, prepared an antihelmintic and compared its efficacy with that of piperazine citrate against *Toxocara vitulorum* in cow and buffalo calves. The preparation comprises of a number of plants including *C. anthelminticum*, the preparation as found to exhibit antihelmintic efficacy lower than that of piperazine citrate, however the preparation was suggested to be used next to piperazine citrate against *Toxocara vitulorum* in cow and buffalo calves [20].

Antihyperglycemic activity

Ani and Naidu, studied the effects of *C. anthelminticum* Kuntze extract containing mixture of polyphenolic compounds, against rat intestinal α-glucosidases, human salivary α-amylase activity and postprandial hyperglycemia in rats. The polyphenolic components of *C. anthelminticum* seed extracts, inhibited rat intestinal disaccharidases in a dose dependent manner. IC_{50} values observed for intestinal sucrase, maltase and *p*-nitrophenyl α-D-glucopyranoside (PNP-glycoside), were found to be 34.1 ± 3.8, 62.2 ± 4.5 and 500.5 ± 11.9 µg of extract, respectively. The inhibitory activity of the extract against human salivary α-amylase was found to be 185.5 ± 4.9 µg. The inhibitory activity of the extract was found to be 8–32 times more potent than DL-catechin, but less active than acarbose on rat intestinal disaccharidases and salivary α-amylase. For maltase, sucrase and PNP-glycoside hydrolysis, the enzyme kinetic studies showed low K_i values, 30.24 µg, 76.67 µg and 341.60 µg of the plant extract, respectively. The in vitro inhibition of glucosidases was further confirmed by in vivo maltose tolerance test in rats. Administration of the extract at 50–200 mg/kg body weight to maltose (2.0 g/kg b.wt), loaded rats significantly reduced the postprandial plasma glucose levels compared with acarbose. The inhibitory components of the extract were determined as a mixture of polyphenolic compounds such as, gallic acid, protocatechuic acid, caffeic acid, ellagic acid, ferulic acid, quercetin and kaempferol. The study suggested that the *C. anthelminticum* exhibit antihyperglycemic effect by reducing postprandial glucose in rats through the modulation of α-amylase and glucosidases (sucrase and maltase) activity and thus may be valuable in the management of diabetes mellitus[3].

Antimicrobial, antibacterial and antifungal activities

Sharma and Mehta, assessed the various extracts of the seeds of *C. anthelminticum* for their antimicrobial potential using the filter paper disk method against several human pathogenic bacteria and fungi. Certain extracts showed significant inhibitory effects against certain bacteria and fungi [21].

Hanif *et al.*, examined the antibacterial and antifungal activities of the essential oils 110 medicinal plants including *C. anthelminticum*, extracted using CO_2 supercritical fluid extraction technology. Varying degrees of activities were observed for most of the plants [22].

Diuretic activity

Shenoy and Shastry, examined the diuretic activity of a certain polyherbal formulations, including a formulation from the aqueous extracts of *C. anthelminticum*. All the animals received a priming dose of 0.9% sodium chloride solution (25 mL/Kg body wt.), the first group served as control and the second group received the standard drug spiranolactone (20 mg/Kg body wt.) in 0.9% sodium chloride solution and third group received the formulation (150mg/Kg body wt.) in 0.9% sodium chloride solution, the volume of the urine was groups

for 5h. For *C. anthelminticum* extract an increase in the volume of urine, sodium and chloride ions was observed, while levels of potassium ions were not changed [23].

Larvicidal activity

Anamika *et al.*, exaimed the petroleum ether extracts of the fruits and leaves of *C. anthelminticum* for larvicidal activity against *Anopheles stephensi*. Both the fruit and leaves petroleum ether extracts indicated significant larvicidal activity against instar larvae with LC_{50} values of 162.60 ppm for the fruit extract and 522.94 ppm for the leaves, after 24 hours. The toxicity of the petroleum ether extract of the fruit was 11.66, 2.15 and 1.32 folds more than that of the toxicity of the leaf extract after 24, 48 and 72 hr, respectively at LC_{90} level, and at LC_{50} level the corresponding values were 3.22, 1.83 and 1.19, respectively. Thus the study suggested the petroleum ether extract of *C. anthelminticum* fruits as a promising source for controlling *Anopheles* larvae [24].

Macrofilaricidal activity

Nisha *et al.*, examined the methanolic extracts of 20 medicinal plants including *C. anthelminticum* at 1-10 mg/ml for in vitro macrofilaricidal activity against adult *Setaria digitata*, using worm motility assay. *C. anthelminticum* and three other plants indicated good macrofilaricidal activity at concentrations below 4 mg/ml and an incubation period of 100 minutes. Complete inhibition of worm motility and subsequent mortality for *C. anthelminticum* was observed at 3 mg/ml. In case of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) reduction assay which was carried out at 1 mg/ml and 4-hour incubation period, *C. anthelminticum* showed 43.15% inhibition in formazan formation as compared to the control [25].

Skin formulations

Shah, developed a formulation of topical cream or ointment for enhancing general health and inhibiting chronic skin disorders such as psoriasis, eczema, lichen planus, Urticaria, neurodermatitis, dryness, inflammation, irritation, rashes, papules, abrasions, and discoloration. The formulation comprises of hydrolyzed ghee (butterfat) and herbal extracts derived from at least two of a number of plants including *C. anthelminthicum.* The formulations are also prepared as decoction and coffee to relive stess, and possess anti-histaminic, anti-inflammatory, anti-infective, anti-fungal properties, and adrenocortical stimulation, cortisol preservation, and control over drying and over secretory action [26].

A formulation for the treatment of skin disorders such as psoriasis, eczema and lichen planus and promoting general health was developed from the plant extracts from a group of plants including *C. anthelminthicum*. The formulation was found to be useful in increasing the rate of healing of chronic skin conditions and reducing the effects of stress and reinforcing the immune response [27].

Shah, reported the preparation for a medication based on a mixture of extracts comprising of the extract of the seeds of *C. anthelminticum*, and the extracts of *Melia Azardiracta* and *Casia tora*. For topical application the extracts were formulated with ghee or sesame oil and in dry form it could be formulated as a decoction, mouthwash and nasal drop. The treatment is suggested to treat acne, impetigo, mycosis and pruritus of the skin [28].

Hashimoto *et al.*, developed a safe formulation for the reduction of pigmentation, such as a pigmented spot by aging or sun tanning, and freckles. The formulation is based on the extracts of one of the five plants including *C. anthelminticum* [29].

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