Ascaridole: A phytochemical of modern medicinal perspective

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ABSTRACT

American wormseed oil, also known as Chenopodium ambrosioides oil, is obtained from the herbs of the genus Chenopodium which comprises more than 200 species and belongs to the geographical region of Asia, Europe, China, India, America and other countries. Chenopodium has been traditionally used for digestive, respiratory, diabetes, uro-genital, nervous and vascular disorders and has antihelminthic, vermifuge, emmenagogue sedative, antipyretic, antihypermic and abortifacient activities. Ascaridole is a bicyclic monoterpene commonly known as ascarisin or 1,4-epidioxy-p-menth-2-ene which have sedative, antifungal and pain-relieving properties. It is a potent inhibitor of Trypanosoma cruzi, Plasmodium falciparum, and Leishmania amazonensis and is well known for its worm-expelling potential. Ascaridole was firstly isolated by a German pharmacist in the 1900’s and at that time it was one of the best antihelmintics for the treatment of ascarids and hookworms in humans and other species like cats, dogs, horses and pigs. Ascaridole could be extracted by using a non-polar solvent hexane due to its very poor solubility in water. From the literature support, it has been proved that ascaridole have very high potential in the modern and other system of medicine for the treatment of various disorders. So on the basic of its uses, here we have collected and compiled all the data regarding its medicinal uses, pharmacological activities and analytical techniques of the ascaridole in the present review and expected that this review will be beneficial for the researcher in the field of medicine and other allied science.

Keywords: Analytical techniques, Antihelminthic, Ascaridole, Chenopodium ambrosioides, Medicinal uses, Pharmacological uses

1. Introduction

Chenopodium ambrosioides L. (C. ambrosioides) is a weedy herb of the genus Chenopodium which comprises more than 200 species and commonly known as Chenopodium oil, goosefoot and American wormseed oil. C. ambrosioides is a natural derived drugs of Europe, Asia, India, China and America and several parts of Chenopodium are mainly used for different types of disorders. Seed and fruit of C. ambrosioides are rich sources of essential oils mainly containing ascaridole as an active phytochemical. Literature search revealed the pharmacological importance of C. ambrosioides which included antihelminthic, vermifuge, emmenagogue sedative, antipyretic, antihypermic and abortifacient properties. It is used in the respiratory, diabetes, digestive, uro-genital, nervous and vascular disorders[1]. Chenopodium oil is known for its anthelmintic property which is mainly because of the presence of ascaridole. Further presence of endoperoxide is essential for its anthelmintic properties. Chenopodium oil contains numerous phytoconstituents, i.e. ascaridole, hydrocarbons, p-cymene, terpinene, limonene, isoascaridole, trans-diol and cis-diol. Ascaridole produces hypothermia and decreases locomotory activity in mice but at high dose level it is lethal for animals. Effect of ascaridole against malaria was also investigated and was found to inhibit the growth of Plasmodium falciparum (P. falciparum)[2]. Ascaridole is also known as ascarisin or 1,4-epidioxy-p-menth-2-ene which is a bicyclic monoterpene. Ascaridole has sedative, antifungal and pain-relieving properties and it is also a potent inhibitor of Trypanosoma cruzi (T. cruzi), P. falciparum, and Leishmania amazonensis (L. amazonensis).

Ascaridole is found to be active on various types of tumor cell lines, i.e. HL60 (human promyelocytic leukemia cells), CCRF-CEM (human leukemia cell lines), MDA-MB-231 (breast cancer cell line). Melaleuca alternifolia oil which is also known as tea tree oil showed contact allergy due to the presence of the significant amount of ascaridole[1,3].
2. Biological activities of C. ambrosioides

C. ambrosioides is an herbaceous plant mainly used in traditional medicine as a condiment by different people of the world. C. ambrosioides belongs to Chenopodiaceae family and grows in South and Central America. C. ambrosioides are mainly used as a kind of anti-tumoral, anti-inflammatory, anthelmintic, vermifuge, emmenagogue, abortifacient and anti-leishmanial drug. Ascaridole is one of the most important constituents of C. ambrosioides which is maximum in the seeds as compared to other parts. Some other phytocomstituents are also present in C. ambrosioides and those are ascaridole-glycol, α-pinene, myrcene, limonene, trans-pinocarveol, α-terpineol aritisone and phellandrene[2,4]. Different species of Leishmania cause cutaneous ulcers which affect a large number of populations in the world and native people are using Chenopodium oil for the treatment of some disorders. Chenopodium oil, a potent anthelmintic, was steam distilled from C. ambrosioides. Ascaridole which constitutes more than 50% of the weight of the oil is mainly responsible for its anthelmintic property[2]. In another study, it has been proven that infusions of C. ambrosioides are safer as a vermifuge as compared to the essential oil[2]. The fruit and seed parts of Chenopodium contain essential oils and ascaridole is main active constituent, and further ascaridole has been attributed to its vermifuge potential[4].

3. Chemical components of C. ambrosioides

An phytochemical analysis revealed that C. ambrosioides contained various types of pure phytochemicals such as limonene, d-camphor, ascaridole, α-pinene, p-cymene, iso-ascaridole, α-terpinene, artisone, butyric acid, ferulic-acid, geraniol, saponins and stigmasterol, etc. Among all the reported phytochemicals, the most active and effective one responsible for the pharmacological activities is ascaridole[5]. Some other active chemicals which are also present in C. ambrosioides are artisone, l-pinocarvone, p-cymol, spinasterol, tartaric-acid, hydroperoxides, terpine, hydrocarbons, vanillic-acid, menthadiene, menthadiene methylsalicylate, terpinyl-salicylate, myrcene, iso-ascaridole, trimethylamine, urease, α-pinene, ascaridole, malic-acid, safrole, terpinyl-acetate, triacontyl-alcohol, trans-diol and cis-diol are derived from ascaridole[2,4].

4. An overview of ascaridole

Ascaridole was known for its vermifuge (worm-expelling) potential and firstly it was isolated by a German pharmacist living in Brazil in 1895. It was one of the main anthelmintics used for the treatment of ascarids and hookworms in humans, dogs, pigs, horses and cats in the early 1900’s. Plants belonging to the Chenopodiaceae are distributed widely in the East Mediterranean and they are often used as drugs and spice agents because of the various useful metabolites. Plants and marine organisms are the main sources of natural peroxides and various peroxides show antimalarial, antitumor, antiviral and antibacterial activities[1]. The growth of P. falciparum was inhibited by ascaridole in vitro, and cineol was found to be inactive due to the lack of internal 1,4-peroxide and artemisinin was active against P. falciparum due to its 1,4-endoperoxide signifying that endoperoxide was essential for its anthelmintic in ascaridole. Ascaridole decreases phasic contractions, reduces basal tone and contractions of rat gastrointestinal tissue in vitro induced by carbachol. Ascaridole is having unpleasant flavor and further it is shock sensitive and could be explosive[2,3]. Ascaridole have sedative, pain-relieving properties and antifungal activity because of the presence of various types of monoterpenes. In guinea pigs, topical application of the oil was found to be effective against ringworm. In some other in vitro studies, ascaridole was found to be active against the tropical parasite, i.e. T. cruzi, and showed strong antimalarial and insecticidal activities[4]. Ascaridole is a bicyclic monoterpane which is present in essential oils of different species of Chenopodium collected from Spain and Slovakia. Ascaridole has anthelmintic, sedative and pain-relieving properties. Ascaridole also show potent inhibitory activity against various organisms such as P. falciparum, T. cruzi, and L. amazonensis and active against different cancer cell lines. Ascaridole, extracted from wormseed oil, exhibited cytotoxic activity against HL60 and CCRF-CEM and MDA-MB-231. Ascaridole is also cytotoxic to human cell lines for colon cancer and leukemia, and inhibits connective tissue cancer in mice[6]. A traditional medicine known as Paico from Peru mainly contains ascaridole as a active principle and shows anthelmintic and antirheumatic potential[7]. Ascaridole is a main active constituent of boldo leaves essential oil and data show that central and northern species have higher percentages of ascaridole as compared to the southern species. Further ascaridole content was found to be less in the wild plants’ leaves as compared to the cultivated plants’ leaves, which revealed that the amount of ascaridole in the plant was not dependent on the genetic factors but the environmental factor[8]. Ascaridole separated from C. ambrosioides was found to be active against P. falciparum[9]. From the study, it was concluded that ascaridole is a delicate molecule and it is also sensitive to chemical attack and thermal shock[10]. Bicyclic endoperoxides such as ascaridole and dihydroascaridole have been reported to exhibit moderate antimalarial properties. A number of diaryl substituted endoperoxides was synthesized and was found to have higher activity as compared to dihydroascaridole and ascaridole[11]. Ascaridole is poor water-soluble compound and could be extracted from aqueous phase to the hexane. Ascaridole synthesised from α-terpinene showed nematocidal activity and was found to be 95% pure mainly confirmed by the nuclear magnetic resonance spectroscopy[12].

5. Pharmacological activities of ascaridole

5.1. Antinociceptive and anti-inflammatory activities of ascaridole

To evaluate the compatibility of ascaridole obtained from C. ambrosioides molecular docking was done with the N-methyl-D-aspartate (NMDA) receptor and the results showed NMDA receptor
binding affinity. In another study, the hydro-alcoholic extract of C. ambrosioides was tested for osteoarthritis and it was found to be effective due to behavioral changes and reduced synovial inflammation in the pain. Furthermore, this study also revealed that this was because of the antagonistic action of ascaridole on the NMDA receptor[13]. Supercritical fluid extraction and hydrodistillation method were used for the separation of volatile oil from Ledum palustre (L. palustre) aerial parts. Then, the anti-inflammatory activities of these extracts were tested by subcutaneous carrageenan induced hind paw oedema model using ketoprofen or piroxicam as a standard drug. The results showed that different fractions of L. palustre essential oil significantly inhibited oedema and the results were almost similar to the standard drugs, piroxicam and ketoprofen[14].

5.2. Anti-leishmanial effects of ascaridole

The anti-leishmanial activity of volatile oil of C. ambrosioides and carvacrol, caryophyllene oxide and ascaridole were evaluated in vivo in BALB/c mice which were infected with L. amazonensis. The essential oil prevented lesion development, whereas it was found to be negative in case of pure components[15]. The anti-leishmanial activity and cytotoxicity of the volatile oil of C. ambrosioides and major compounds including ascaridole was evaluated. Further its effect against bacteria, fungi and protozoa were also evaluated in this study. All the tested components were found to be active against Leishmania with reference to amastigote and promastigote forms. Ascaridole was found to have better activity and the essential oil was found to have the highest selectivity index[16]. Effect of ascaridole with caryophyllene oxide and carvacrol isolated from C. ambrosioides was evaluated in BALB/c mice against L. amazonensis. Combination of ascaridole and carvacrol was found to be effective against promastigotes mainly due to its synergistic effect, while some activities were also observed in case of ascaridole-caryophyllene oxide but it was found to be unsympathetic. Further, mice treated with the ascaridole-carvacrol showed significant differences in lesion size and parasite burden as compared to the control group[17].

5.3. Anti-trypanosomal, larvicidal and nematicidal activities of ascaridole

Amebiasis is a parasitic disease in developing countries. Amebiasis activity of the volatile oil of Dysphania ambrosioides (L.) was evaluated by both In vitro and in vivo method and was found to be active. Further, oral treatment of infected hamster with essential oil was also cured up to significant level. Chemical analysis signified the presence of ascaridole as a main active component[18]. Four monoterpene hydroperoxides along with ascaridole were isolated from the aerial parts of C. ambrosioides. Ascaridole and these monoterpene hydroperoxides were tested against epimastigotes of T. cruzi and were found to be effective[19]. Essential oils and isolated products of leaves of Croton regelianus (C. regelianus) growing in two different regions at Ceará State were tested against Meloidogyne incognita, Aedes aegypti and Artemia sp. From the bioassay it was found that the pure component ascaridole and essential oil were found to be active against Meloidogyne incognita, but the effectiveness were found to be the most against both Aedes aegypti and Artemia sp. larvae[20].

5.4. Anticancer activity of ascaridole

Antitumor effects of ascaridole and essential oil obtained from of leaves of C. regelianus were evaluated and were found to be active in terms of the cytotoxicity. Ascaridole showed antitumor activity in sarcoma 180 murine model which signified the ethnopharmacological use of this plant for the treatment of cancer[21]. Fifty three phytochemicals isolated from plants were tested for their differential cytotoxic effects in the cell lines which were having defect in the nucleotide excision repair genes ERCC6 or XPC, and from the result it was found that ascaridol was the most effective[22]. Effects of ascaridol isolated from a commercial preparation of Chenopodium oil against tumor cell lines, i.e. HL60, CCRF-CEM, MDA-MB-231, were investigated in vitro, and from the result it was found that ascaridol had an antineoplastic activity[23].

5.5. Effect of ascaridole on eczema

Three hundred and nineteen patients with eczema were selected for the determination of the effect of ascaridole through optimal patch test and relationship between a positive reaction to ascaridole and a positive reaction to oxidized tea tree oil were also investigated. Results showed that as concentration increases the frequency of positive reactions also increased[24].

5.6. Antimalarial activity of ascaridole

Effects of ascaridole on P. falciparum were investigated and it was found that ascaridole inhibited the growth of plasmodium after 3 days. From the result, it was also found that lower concentrations mainly affected trophozoite stage whereas the ring stage was marginally affected. Further, cineol having epoxide group instead of the peroxide group found in ascaridole was found to be inactive, which revealed that peroxide group is essential for the antimalarial activity[9].

5.7. Effect of ascaridole on skin sensitivity

Penetration enhancers effect of cyclic terpenes and their oxides ascaridole towards 5-fluorouracil by the use of excised human epidermal membranes was investigated. Skin data showed that terpenes had various types of activities and Chenopodium which contained more than 70% of ascaridole was found to be less effective as compared to the isolated terpenes[28]. Effectiveness of cell line THP-1 as compared to monocyte-derived dendritic cells was evaluated using a known potent sensitizer 2,4-dinitrochlorobenzene and the terpenoid ascaridol[26]. In another study, effects of ascaridole...
on protein reactivity and dendritic cell activation were studied. From the result, it was found that maturation was accompanied by the release of proinflammatory cytokines, tumor necrosis factor-α, interleukin (IL)-6, IL-1β, and IL-8. Further radical formation may be involved in the skin sensitization[27].

5.8. Toxicity study of ascaridole

To investigate the mechanistic study of the toxicity of the essential oil and their pure ingredients ascaridole, carvacrol, carophyllene oxide mammalian cells and mitochondria were used. Without Fe\(^{2+}\), ascaridole was found to be less toxic to mammalian mitochondria as compared to other components. Further, Fe\(^{2+}\) potentiated the toxicity of ascaridole on oxidative phosphorylation of rat liver mitochondria and ascaridole in peritoneal macrophages from BALB/c mice exhibited more significant results in terms of toxicity as compared to the isolated mitochondria[28].

5.9. Effect of ascaridole as potential fumigant

For the development of the better and potential natural insecticides against cockroaches, volatile oil of Chinese *C. ambrosioides* and their main active ingredients were evaluated. From the result, it was found that the essential oil and pure components isoascaridole, (Z)-ascaridole, and p-cymene have fumigant toxicity against the tested cockroaches. Further, topical application bioassay also showed that these components were toxic against cockroaches and (Z)-ascaridole epoxide and some other phytoconstituents were present in the extracts as a chief component[14].

Phytochemical analysis of the volatile oil of *Dysphania ambrosioides* (L.) was performed to know the chemical profile and from the result it was found that it contained ascaridole as a main component[18]. Hydrodistillation process was used for the separation of volatile oils of *Cymbopogon citrates*, *Cymbopogon schoenanthus*, *Securidaca longepedunculata*, *C. ambrosioides*, *Cochlospermum tinctorium*, *Cochlospermum planchonii* and *Cymbopogon giganteus*, and further their chemical characteristics were checked by GC-MS technique. Ascaridole was found to be the major active constituent in *C. ambrosioides*[34]. Hydrodistillation method was used for the separation of essential oil from the leaves of *Curcuma longa* L. and further it was subjected to GC-MS technique to know their chemical constituents. The GC-MS analysis of oil showed the presence of 25 constituents and out of them eucalyptol was found to be the chief constituent. Ascaridole epoxide and some other phytoconstituents were also present in considerable amount[35]. Hydrodistillation method was used for the separation of the essential oils of the leaves of *Artemisia vulgaris*, *Artemisia indica* and *Artemisia dubia* and GC-MS method was used for their analysis. *Artemisia indica* oil was found to contain trans-p-mentha-2,8-dien-1-ol, ascaridole, iso-ascaridole and trans-verbolen[36]. GC-MS technique was used for the determination of the chemical composition of volatile oil of *C. ambrosioides*. Twenty-two components were found to be present in the essential oil whereas p-cymene, (Z)-ascaridole, iso-ascaridole and piperitone were found to be present in the significant level[39]. Hyphenated GC-MS method were used to know the chemical constituents of dichloroethane, n-hexane, ethyl acetate, chloroform, methanol, and 60% ethanol root extracts of *Rhodiola imbricata* Edgew. Chemical analysis of the root extracts revealed the presence of 63 phytochemicals including ascaridole as a major component[37]. GC-MS method was used for the determination of the chemical profile of the volatile oils of *C. ambrosioides*. The chemical profile showed that the major components presented in the *C. ambrosioides* were p-cymene, α-terpinene and ascaridole[38]. Capillary gas chromatography-flame ionization detector and GC-MS techniques were used for the determination of the phytochemicals of the essential oil of *Drimys winterii* and *Peumus boldus*. p-Cymene, ascaridole and 1,8-cineole were found to be present in the major portion and even though more than 96%[39].

For the detection of ascaridole in the Australian tea tree oil (*Melaleuca alternifolia*), multi heart-cut multidimensional gas chromatographic system coupled with mass spectrometer and by
conventional enantio-GC was used and further method validation was also carried out for monitoring the repeatability of the traditional one-dimensional peak detection, routine application, two-dimensional peak detection, limit of detection and limit of quantification[31]. GC and GC-MS chemical profiling of the hydrodistilled volatile oil from Tanacetum macrophyllum and Achillea grandifolia Friv through Clevenger-type apparatus revealed the identification of more than 215 components, and ascariolide, α-thujone, camphor, borneol and (Z)-jasmone were found to be the chief active constituents whereas borneol, 1,8-cineole, camphor, copaborneol, isobornyl acetate and γ-eudesmol were found to be in the Tanacetum macrophyllum oil[40]. Hydrodistilled volatile oil of the C. ambrosioides has been subjected to isolation process and analyzed by GC-MS method. Ascaridole, p-cymene and α-terpinene were found to be present as chief components in the sample[41]. GC-MS technique was used for the determination of the ascariolide in leaves of medicinal plants of the genus Chenopodium and ascariolide was found to be present as the chief active constituent in the form of peroxy monoterpenoid. Further, three minor isomers cis-isascaridole, trans-isascaridole and trans-ascaridole were also detected[42]. GC-MS method was used for the determination of ascariolide in rat plasma using naphthalene as an internal standard. Ethyl acetate was used for the separation of the samples from plasma and further separated by GC method using HP-5MS capillary analytical column and quadrupole mass spectrometer operated in ion monitoring mode[43]. Variation of total alkaloid concentration and essential oil components of Boldo tree of southern, northern and central parts were studied. Ascaridole content of the volatile oil was found to be the highest in the north population and p-cymene was found to be the most in cases of south population[44]. GC, GC-MS and carbon-13 nuclear magnetic resonance techniques were used for the determination of the components of the commercial sample of C. ambrosioides of Madagascar, p-Cymene, ascariolide, α-terpinene, iso-ascaridole and limonene were found to be present in significant levels in the tested samples[45].

GC and GC-MS method were used for the determination of the chemical components of the Artemisia molinieri aerial parts and among the 69 compounds the major components were 1,8-cineole, α-terpinene, ascariolide, p-cymene and germacrene D[46]. Isolation of the main component of “Paico”, another name of C. ambrosioides, and “Aritasou”, the Japanese name of C. ambrosioides, was performed and ascariolide was found to be the main active principle in both samples[7]. Optical activity and chromatographic resolution of naturally occurring ascariolide and several synthetic derivatives were evaluated and the results showed that C. ambrosioides and Peumus boldus produce have ascariolide in racemic form[47]. GC-MS method was used for the determination of the essential oil composition of the C. ambrosioides prepared through hydrodistillation process and five active components p-cymene, 2-carene, (Z)-ascaridole, iso-ascaridole and α-terpinene were found to be present in the C. ambrosioides[30]. In another study, ascariolide and other monoterpene hydroperoxides were isolated from C. ambrosioides and further the structures of these monoterpene were determined through spectroscopic methods and chemical correlations[19]. GC-MS and gas chromatography-flame ionization detector methods were used for the determination of the chemical composition of the leaf essential oil of C. regelianus collected in Brazil. Twenty monoterpenoids including p-cymene, ascariolide and camphor were identified and quantified as major active constituents[20]. Gastro-floating tablets of ascariolide were prepared and developed for prolong the gastric residence time and therapeutic efficacy. Direct compression techniques were used for the preparation of the tablets whereas content uniformity, friability, weight variation and hardness parameter were taken for their evaluation. Further, drug release behaviors, total floating time, floating lag time were also evaluated during the study[48].

7. Conclusion

Human being and other species need natural products for their better growth, development and reproduction. Before these era, people mainly depend on the herbal medicines for the treatment of disorders on their own believes that these herbal drugs have less side effects and more economic values. A huge number of people of different countries used traditional products for their primary health care since very long time ago. Many synthetic components which are used as medicines have been derived from plants, minerals and organic matter. The World Health Organization has listed various types of plant products and their materials as drugs due to their beneficial medicinal properties. Plants contain huge number of phytochemicals categorized into primary and secondary metabolites are mainly responsible for various pharmacological activities[49-53].

For the treatments of intestinal worm infections, C. ambrosioides has been used in America for long time ago and volatile portion of this drug contains significant amount of ascariolide, which has already been proven as one of the best and potent anthelmintic. Ascaridole is one of the major components of C. ambrosioides which is responsible for its nematocidal activity[2]. Various forms of preparation such as decoctions and infusions of various parts of the plants like inflorescences, leaves, roots of C. ambrosioides and related species have been used for centuries as a traditional anthelmintics and dietary condiments by native peoples against intestinal worms. Ascaridol and commercial preparations of oil of Chenopodium were mainly used for the treatment of intestinal worms[54].

Due to the presence of diverse phytoconstituents, many medicinal plants have different pharmacological activities and could be used as starting materials for developing better and safer drugs of new classes. Various types of currently used drugs are derived from natural sources and people use plants as dietary supplements even without knowing their mode of action. Hence, there is a need of more investigative reports and evidence-based support along with laboratory support for their pharmacological activity and safety issue[55,56]. From all the compiled data, we can conclude that ascariolide has a huge number of potential in the field of medicine, pharmaceutical, agriculture and many more, so it could be used as a remedy for the treatment of various complications of human being.
and other species in the future. The present review summarizes all the needed information regarding its general properties, the sources of this unique phytoconstituent, ancient uses, medicinal uses, pharmacological activities, analytical aspects and other scientific data. So, from all these discussions we can finally conclude that the overall compiled information written in this review paper will be beneficial to the communities of the modern medicine and related areas.

Conflict of interest statement

I declare that I have no conflict of interest.

Acknowledgments

The author wants to acknowledge Banaras Hindu University, Varanasi for online article support.

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