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REVIEW ARTICLE

A Review of Botany, Phytochemical, and Pharmacological Effects of *Dysphania ambrosioides*

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ABSTRACT

Traditional medicine is widely used worldwide due to its benefits and healthier components that these natural herbs provide. Natural products are substances produced or retrieved from living organisms found in nature and often can exert biological or pharmacological activity, thus making them a potential alternative for synthetic drugs. Natural products, especially plant-derived products, have been known to possess many beneficial effects and are widely used for the treatment of various diseases and conditions. *Dysphania ambrosioides* is classified as an annual or short-lived perennial herb commonly found in Central and South America with a strong aroma and a hairy characteristic. Major components in this herb are ascaridole, *p*-cymene, α-terpinene, terpinolene, carvacrol, and trans-isoascaridole. Active compounds isolated from this herb are found to exert various pharmacological effects including schistosomicidal, nematicidal, antimalarial, antileishmanial, cytotoxic, antibacterial, antiviral, antifungal, antioxidant, anticancer, and antibiotic modulatory activity. This review summarizes the phytochemical compounds found in the *Dysphania ambrosioides*, together with their pharmacological and toxicological effects.

Keywords: *Dysphania ambrosioides*; phytochemicals; pharmacological effect; secondary metabolites; toxicity

INTRODUCTION

Natural products have been used by a wide spectrum of populations to alleviate and treat diseases. They can be retrieved from plants, animals, microorganisms, or marine organisms. Natural products such as Traditional Chinese Medicine (TCM), Ayurveda, Kampo, Traditional Korean Medicine (TKM), and Unani are used in alternative medicines (Yuan, Ma, Ye & Piao, 2016). Those traditional medicines have been widely practiced globally for hundreds or even thousands of years. In 1805, the first pharmacologically-active compound, morphine, was isolated from plants by Serturner (Krishnamurti & Rao, 2016). Afterward, numerous active compounds have been identified and isolated from abundant plants available in nature. Traditional medicines nowadays still play a key role in many countries as complementary, alternative, or ethnic medicine. They could provide anticancer, antihypertensive, antimigraine, hepatoprotective effects, and much more. Nevertheless, the adverse effects generated from them shall be reduced to ensure their safety (Yuan, Ma, Ye & Piao, 2016).

Dysphania ambrosioides, also known as *Chenopodium ambrosioides*, is commonly known as Indian wormseed, sweet pigweed, or Mexican tea. It is a hairy, strongly aromatic, annual, or short-lived perennial herb that usually grows wild in Central and South America (Soares *et al*., 2017). The stem of the plant is equipped with glandular trichomes that secrete essential oils (Fatokun *et al*., 2019). According to Soares *et al.* (2017), it is traditionally used as a flavoring agent in various kinds of dishes due to its pungent flavor. It is cultivated in sub-tropical and sub-temperate regions, mostly used for consumption in the form of leafy vegetables or herbs. The same report also stated that in Brazil, *D. ambrosioides* is known as 'erva de Santa Maria', which the infusion of the leaves can be used as a vermifuge. The study mentioned that this plant's essential oil is used for pharmacological purposes because of its high ascaridole content. Besides ascaridole, based on the chemotypes, *D. ambrosioides* essential oil contains other monoterpenes, such as p-cymene, α-terpinene, γ-terpinene, terpinolene, carvacrol, and trans-isoascaridole (Barros *et al*.,2019) as the major compounds as well as other compounds, such as o-cymene, trans-beta-terpinyl butanoate, and D-limonene (Soares *et al*., 2017). This review paper discusses the bioactive constituents of *D. ambrosioide*s, along with its pharmacological and toxicological properties and suggested mechanisms of actions.

Figure 1. *Dysphania ambrosioides* (L.) Mosyakin & Clemants Mexican tea (Mohlenbrock, 1992).

Botanical Description

Domain	: Eukaryote
Kingdom	: Plantae
Division	: Spermatophyta
Subphylum	: Angiospermae
Class	: Dicotyledonae
Order	: Caryophyllales
Family	: Chenopodiaceae
Genus	: Dysphania
Species	:*Dysphania ambrosioides*

Plant Morphology

D. ambrosioides is a highly branched herb that can reach up to 1 meter high (Albuquerque, Patil, & Máthé, 2018). Its leaves are alternate, elongated, with acute apex, jagged edges, hairy, with different sizes, where the smaller ones are on the top of the plant and are sessile; the larger ones are at the bottom with a short petiole (Blanckaert *et al*., 2011). Moreover, it has a strong and characteristic smell. *D. ambrosioides* has a racemose type of inflorescence, presented as green colored small flowers (Sá *et al*., 2016). Each cluster of flowers usually has 3-5 sepals, partially or united, with 3-5 stamens, free or with adnate filaments, on each sepal. It also has numerous, spherical, black colored seeds that are surrounded by a persistent calyx that is less than 0.8 mm long (Fatokun *et al.*, 2019).

Plant Distribution

Native to Central and South America, *D. ambrosioides* is originated from Mexico. Usually, its growth is spontaneous mainly in America and Africa due to its subtropical and tropical regions, and also in temperature zones ranging from the Mediterranean to Central Europe. The distribution of *D. ambrosioides* is extensive in Brazil, which occurs in almost all territory (Sá *et al*., 2016).

SECONDARY METABOLITES OF *D. AMBROSIOIDES*

Thirumurugan *et al.* (2018) said that plants synthesize their secondary metabolites for self-protection and self-regulation. The same report stated that the plant metabolites have relevant biological and organoleptic properties, which can play important roles in human health and general well-being. Studies have discovered that *D. ambrosioides* contains ascaridole, tannins, flavonoids, kaempferol, cardiotonic, anthraquinone, alkaloids, rutin, ethyl acetate, n-heptacosane, n-hentriacontane, n-butanol, n-docosane, aritasone, camphor, *p*-cymene, p-cimol, β-pinene, pinocarvone, β-caryophyllene, geraniol, γ-gurjunene, γ-terpineol, α-terpineol, α-terpinene, spinasterol, safrole, thymol, terpinyl-salicylate, terpinyl-acetate, triacontyl-alcohol, quercetin, and chrysin among others (Pedro *et al.*, 2019; Jesus *et al*., 2018; Albuquerque, Patil, & Máthé, 2018)

Essential Oils (EO)

The EO of *D. ambrosioides* was reported to contain δ-3-carene, α-terpinene, p-cymene, limonene, γ-terpinene, p-cymen-8-ol, ascaridole, cis-piperitone oxide, trans-piperitone oxide, trans-ascaridolyglycol, thymol, carvacrol, isoascaridole, and β-ionone based on GC-MS analysis (Zefzoufi *et al*., 2019). The EO of *D. ambrosioides* was found to be pale yellow to orange-yellow liquid, with a peculiar, unpleasant smell and a bitter, burning taste (Shah & Khan, 2017).

Extract

According to Ferreira *et al*. (2019), flavonoids, as rutin equivalent, are abundantly found in the aerial parts of *D. ambrosioides* rather than other phenolic compounds. This study has been done through spectrophotometric analytical methods. While another study by Shah and Khan (2017) extracted some compounds from *D. ambrosioides* using methanol, followed by further fractionation using several solvents. The results were: stigmasterol, β-sitosterol, and octadecanoic acid from ethyl acetate subfraction; scopoletin from dichloromethane subfraction; and 1-piperoylpiperidine from n-butanol subfraction. A study done by Zohra *et al*. (2018) showed that extraction using methanol was the best way to extract the phytochemical contents of *D. ambrosioides*.

BIOLOGICAL AND PHARMACOLOGICAL EFFECTS OF *D. AMBROSIOIDES*

The EO of *D. ambrosioides* obtained from the whole plant, including the fruit or the aerial parts of the plants, has been traditionally used in many ways. In Cameroon, it is commonly used to repel and kill insects due to the presence of monoterpene peroxide ascaridole and aromatic *p*-cymene (Pavela *et al*., 2017). Moreover, it has been observed to possess antibacterial, antiviral (Zefzoufi *et al*., 2019), antileishmanial, cytotoxicity, anticancer (Zohra *et al*., 2018), antiprotozoal towards *Plasmodium falciparum*, antiparasitic (Pizzorno, Murray, & Joiner-Bey, 2016), and anthelmintics activity (Ortner & Buikstra, 2019). The EO of *D. ambrosioides* was also reported to have antibiotic modulatory (Almeida *et al*., 2019) and antioxidant activity (Brahim *et al*., 2015). Furthermore, some studies stated that this plant might show schistosomicidal (Soares *et al*., 2017) and nematicidal effects (Faria *et al*., 2016).

Schistosomicidal Activity

Schistosomiasis is recognized as one of the most prevalent parasitic diseases globally, second in rank after malaria (Hajissa *et al*., 2018). This parasitosis is caused by the genus Schistosoma of trematode parasites. Praziquantel (PZQ) has been used to treat schistosomiasis for many years. However, several studies have reported the diminishing efficacy of this drug due to some strains that are resistant to PZQ (Wakabayashi *et al*., 2015; Gouveia *et al*., 2018). This led to the study of *D. ambrosioides* to investigate and assess its schistosomicidal effects toward *Schistosoma mansoni*. According to the *in vitro* study done by Soares *et al*. (2017), EO of *D. ambrosioides* showed promising and significant schistosomicidal activity against *Schistosoma mansoni* adult worms, in which at a concentration of 25 µg/mL and 12.5 µg/mL it succeeded to kill 100% of worm pairs in 24 and 72 hours, respectively. In respect to 24, 48, and 72 hours, it had LC_{50} values of 6.50 ± 0.38, 3.66 ± 1.06, and 3.65 ± 0.76 µg/mL. Besides, *D. ambrosioides* EO displayed much higher activity compared to other EOs, such as *Foeniculum vulgare* Mill. EO, which only exerted significant activity at concentrations equal to 100 µg/mL or higher. However, it showed lower activity compared to PZQ. Nevertheless, EO of *D. ambrosioides* is still a promising alternative treatment for Schistosomiasis conditions.

Nematicidal Activity

Barros *et al*. (2019) reported that *D. ambrosioides* oil at a concentration of 500 µg/mL caused more than 90% second-stage juveniles (J2) mortality of *Meloidogyne incognita*, with LC_{50} and LC_{95} values of 307 µg/mL and 580 µg/mL, respectively. The study found that significant reduction of J2 hatching and toxicity toward *M. incognita* eggs were shown at 1,100 µg/mL. The same study also reported that (Z)-ascaridole, isoascaridole, and *p*-cymene are the active compounds responsible for its nematicidal activity towards *Meloidogyne incognita.* Another *in vitro* study from Faria *et al*. (2016), reported that the EO from the aerial parts of this plant was able to induce around 90% hatching inhibition of *Meloidogyne chitwoodi* with EC_{50} of less than 0.15 µl/mL. The author stated that the hatching inhibition of *Meloidogyne chitwoodi* was due to the presence of ascaridole, isoascaridole, carvacrol, methyl salicylate, *p*-cymene, and *γ*-terpinene in the EO.

Insecticidal Activity

A study by Arena *et al.* (2018) stated that *D. ambrosioides* EO exerted insecticidal activity toward *Alphitobius diaperinus*, the darkling beetle, with LC_{50} value of 17.74 µg/cm^2 and LC_{100} value of 40 µg/cm^2. Whereas, Pavela *et al*. (2017) found that the EO of *D. ambrosioides* was toxic to adults of *Musca domestica,* commonly known as a housefly, with LD_{50} value of 51.7 µg/adult. The EO displayed an IC_{50} value of 77 µg/mL for AChE, and the author believed that inhibition of AChE might be the underlying mechanism of action for its toxic effect against *M. domestica.* In an experiment conducted by Langsi *et al.* (2018), EO of *D. ambrosioides* was combined with EO of *Cupressus sempervirens* for their insecticidal potential towards *S. zeamais* present on stored maize. The study noted that after 14 days of storage, 25:75 and 75:25 ratio combinations of both EOs resulted in 80% mortality, while 50:50

ratio combinations resulted in 100% mortality of *S. zeamais.*

Antimalarial Activity

Malaria has been a challenge to global public health, with approximately 228 million cases, and 405,000 deaths were reported worldwide in 2018 (World Health Organization, 2019). According to Cysne *et al*. (2016), the hydrochloric crude extract (HCE) of *D. ambrosioides* was found to be able to exert a moderate antimalarial activity towards *Plasmodium falciparum* cultures. The study noted that the HCE exerted an antiplasmodial activity and inhibited the parasite growth in a dose-dependent manner with IC_{50} of 25.4 µg/mL. Another study was reported that the ascaridole in HCE was a potent inhibitor of the *P. falciparum* (Albuquerque, Patil, & Máthé, 2018). Aside from HCE, ascaridole can also be isolated from the EO of the plant and in the hexane fraction of the plant (Fatokun *et al*., 2019).

Antileishmanial Activity

Protozoan parasites of the Leishmania genus are known to cause a group of tropical diseases known as leishmaniasis (Machín *et al*., 2019). According to the study by Shah *et al*. (2015), n-hexane leaves extracts of *D. ambrosioides* at 1 mg/mL displayed 41.2 ± 0.45% mortality of *Leishmania tropica*, species of flagellate parasites. The same study also reported that the ethanol-n-hexane and ethanolic extract of *D. ambrosioides* stem at a concentration of 1 mg/mL exerted leishmanicidal activity, which caused 50.13 ± 0.76% mortality, while the ethanolic root extract showed leishmanicidal activity with 92.51 ± 0.94% mortality of *Leishmania tropica*. The ability of *D. ambrosioides* to display antileishmanial activity is believed to be attributed to the presence of quercetin as the major active compound (Zohra *et al*., 2018).

Immunostimulatory Activity

A study by Rios *et al.* (2017) reported that the hydroalcoholic crude extract (HEC) of *D. ambrosioides* and its hexane fraction (HEF) showed a modulatory effect on the immune response with the activation of phagocytes at the infection site. The report discussed about the induced phagocyte activation, determined by the increased secretion of H_2O_2 and NO by the phagocytes. However, it did not mention about the bioactive compound responsible for the immunostimulatory activity of the extracts; thereby further studies are needed.

Antibacterial Activity

Fatokun *et al*. (2019) found that high concentration (100-200 µL/mL) of *D. ambrosioides* EO was required to exhibit antibacterial activity against Gram-positive S.*aureus* and Gram-negative *P. aeruginosa*, while inhibition of Gram-negative *E. coli* and Gram-positive *B. subtilis* only required concentration as low as 10-20 µL/mL. The study reported that the EO displayed great efficacy at a concentration of 200 µL/mL towards *E. coli, S. aureus,* and *B. subtilis* with the zone of inhibition diameter ranging from 27.5 to 30 mm. In contrast, lower efficacy was shown in *P. aeruginosa* with an 11 mm diameter zone of inhibition. Moreover, the study showed that both Gram-negative and Gram-positive bacteria showed similar sensitivities, and *D. ambrosioides* EO has been suggested as a potent antimicrobial with comparable or even better activity than standard antibiotics, such as ciprofloxacin, ampicillin, vancomycin, and amoxicillin. The author believed that the antimicrobial activities of the EO were attributed to several constituents, namely ascaridole, cymene, ascaridole epoxide, and limonene diepoxide, which are found in *D. ambrosioides.* However, other references, including a study by Santiago *et al*., (2016), stated that *D. ambrosioides* EO was more effective towards Gram-negative bacteria compared to Gram-positive bacteria due to Gram-positive's thicker polysaccharide cell wall that reduces the absorption of antimicrobial agents.

A study conducted by Brahim *et al*. (2015), showed that the EO of *D. ambrosioides* produced zone of inhibitions with the diameter range of 15.33-21.5 mm for Gram-positive bacteria and 7.17-19.17 mm for Gram-negative bacteria. MIC values were reported to be in the range of 1.25 to 5 mg/mL and 0.31 to 20 mg/mL with respect to Gram-positive and Gram-negative bacteria. However, *K. pneumoniae* and *P. aeruginosa* (Gram-positive) were found to be less sensitive to the EO compared to *B. cereus* and *M. luteus* (Gram-negative). In contrast, Gram-negative *E. coli* was the most susceptible and was inhibited at 0.31 mg/mL. Different from previous reports, a study done by Mokni *et al*. (2019) showed that the EO of *D. ambrosioides* exhibited strong inhibition activity in the proliferation of Gram-negative *P. aeruginosa* and Gram-positive *B. subtilis* with MIC values of 0.019 mg/mL for both types of bacteria. In addition, the same study stated that the EO of *D. ambrosioides* had weak inhibition activity toward *B. anthracis* with an MIC value of 0.156 mg/mL.

In accordance with Nguta *et al*. (2016), *Mycobacterium tuberculosis* subsp. tuberculosis 10 and *M. tuberculosis* strain H37Ra were inhibited by hydrochloric crude extract of *D. ambrosioides* leaves with MIC values of 10,000 and 5,000 µg/mL, respectively. This indicated that *D. ambrosioides* EO might be a potential treatment for tuberculosis. The EO of *D. ambrosioides* was also found to have antibacterial activity against *Helicobacter pylori,* which is the cause of gastritis and stomach ulcer (Albuquerque, Patil, & Máthé, 2018).

Antiviral Activity

Viral infections have always been an issue around the world due to its complexity. An example of a common virus is the coxsackievirus, which is a class of enterovirus. Coxsackievirus is divided into group A and group B with twenty-three serotypes in group A and six serotypes found in group B (Murray, Rosenthal & Pfaller, 2015). According to the same report, Coxsackievirus B4 (CVB4) is one of the six serotypes of the coxsackievirus group B. It was stated that, in general, coxsackievirus group B is associated with diseases such as paralytic disease, encephalitis, meningitis, carditis, neonatal disease, pleurodynia, rash disease, respiratory tract infection, and fever. In addition, more uncommon diseases associated with the coxsackievirus group B are diabetes, pancreatitis, and orchitis. In regards, Mokni *et al*. (2019) reported that the EO of Tunisian *D. ambrosioides* showed a prominent *in vitro* antiviral activity with IC_{50} of 21.75 µg/mL against CVB4 with a high selectivity index value equal to 74.34. Although the exact mechanism is still unknown, it was hypothesized that the antiviral activity might be attributed to the presence of cis-ascaridole, which is the main constituent found in the EO.

Antifungal Activity

A study by Juliana *et al*. (2015) displayed that the EO of *D. ambrosioides* at 1000 ppm inhibited mycelial growth of *B. cinerea,* a necrotrophic fungus, by 59.8% and its growth rate by 52.3%. The study noted that the germination of spores was also inhibited up to

96 hours' post-treatment with EO with germination reduction of 58.3%, 48.1%, and 48.3% at 48, 72, and 96 hours respectively. That study also found that ascaridole, thymol, and carvacrol were the components responsible for the antifungal activity against *B. cinerea.*

Brahim *et al*. (2015) reported the promising anticandidal activity of *D. ambrosioides* EO with inhibition zone diameters in the range of 14.67-20 mm and MIC ranging from 0.075-2.5 mg/mL, in which *C. albicans* showed the lowest MIC value among others. Similarly, Mokni *et al*. (2019) also reported that *D. ambrosioides* showed significant antifungal activity toward *C. albicans* with MIC value of 0.039 mg/mL. It was stated that at a concentration of 50 ppm, the EO of *D. ambrosioides* showed significant fungicidal properties against dermatophytes *Microsporum audouinii* and *Trichophyton mentagrophytes*.

Another study by Nitsch-Velásquez (2020) reported that *D. ambrosioides* sterile–essential–oil–less aqueous extract (SALAEL–Da) was able to exhibit moderate fungistatic activity and inhibited the growth of *C. albicans* clinical isolates at 135 mg/mL agar concentration. The report stated that the oxygenated terpenoids including phenolic and alcoholic terpenes were the major compounds that possessed greater antimicrobial activity among other components found in SALAEL–Da. Zetzoufi *et al*. (2019), showed antifungal activity of Moroccan *D. ambrosioides* EO towards *Fusarium culmorum, Fusarium oxysporum* f. sp *melonis*, and *Verticillium dahliae* in which 78-90% radial growth inhibition was observed at a concentration of 500 µg/mL. According to that study, the antifungal activity of *D. ambrosioides* might be due to its low molecular weight components and lipophilic nature that are able to inactivate fungal enzymes, disrupt the cell membrane, and thus cause cell death or sporulation inhibition.

Antioxidant Activity

Brahim *et al*. (2015) found that *D. ambrosioides* EO has moderate to high antioxidant effect when tested by DPPH free radical assays, β-carotene/linoleic acid bleaching, and reducing power determination. The study displayed radical scavenging activity with an IC_{50} value of 4×10^3 g/mL in DPPH, lipid peroxidation inhibition activity with an IC_{50} value of 3.03 g/mL in β-carotene/linoleic acid bleaching test, and electron donor ability with an IC_{50} value of 6.02 µg/mL in reducing power assay. Brahim *et al.* also stated that the promising antioxidant activity of the EO might be attributed to the high portion of *α*-terpinene, which is facilitated by the presence of activated methylene groups.

Tauchen *et al*. (2018) reported that *D. ambrosioides* extract displayed an antioxidant effect on a wide spectrum of cancer cells with a DPPH value of 80.6 µg Trolox Equivalents (TE)/mg extract. Another study by Almeida *et al*. (2019) stated that low antioxidant activity was exerted by *D. ambrosioides* EO at concentrations above 1,024 µg/mL. Study conducted by Villalobos-Delgado *et al*. (2017) performed antioxidant activity evaluation of *D. ambrosioides* infusion (EI) and ethanolic extract of *D. ambrosioides* (EE) against raw ground pork kept at 4 °C for 9 days. The study measured the total flavonoid content (TFC), total phenolic content (TPC), and antioxidant activity (AA) of EI and EE. The report mentioned that the extract had a slightly lower pH than the infusion with values of 6.9 and 7.34, respectively. It was also noted that EI displayed higher TPC (193.50 mg gallic acid equivalent (EAG)/100 g dry weight) and TFC (380.87 mg quercetin equivalent (EQ)/100 g dry weight) compared to EE with values of 126.30 mg EAG/100 g dry weight and 147.26 mg EQ/100 g dry weight, for TPC and TFC accordingly. Meanwhile, for the antioxidant activity, the author found that both EE and EI showed no significant differences in % inhibition with values of 13.63% and 16.65%, respectively.

Antibiotic Modulatory Activity

A study conducted by Almeida *et al*. (2019) tested the antibiotic modulating effect of *D. ambrosioides* EO against *P. aeruginosa, E. coli,* and *S. aureus.* They reported that the EO modulated the effect of imipenem, gentamicin, and norfloxacin towards *P. aeruginosa* positively, in which the concentration of antibiotic required to inhibit bacterial growth was decreased. However, a positive modulatory effect was only found when the EO combined with norfloxacin and imipenem for *E. coli* and *S. aureus*, respectively. Another study conducted by Limaverde *et al*. (2017) showed that the EO of *D. ambrosioides* leaves had potentiating action when combined with antibacterials, which focused on the inhibition of the efflux pumps of *S. aureus* IS-58 strain.

Anticancer Activity

Tauchen *et al*. (2018) reported that *D. ambrosioides* methanol extract strongly exhibited an anti-proliferative effect on a broad spectrum of cancer cells with ORAC (Oxygen Radical Absorbance Capacity) value of 687.3 µg TE/mg extract, and IC_{50} value of 129.2, 69.9 and 130.6 µg/mL for Caco-2, HT-29 and Hep-G2 cell lines, respectively. It was also noted that phenolic compounds and alkaloids content of the extract were important for its anticancer activity. Another study was done by El Yahyaoui El Drissi *et al.*, (2017) found that in Morocco, *D. ambrosioides* is traditionally used to treat tonsil cancer. Meanwhile, a study done by Zohra *et al.* (2018) used human hepatoma cell lines to evaluate the anticancer activity of *D. ambrosioides* leaves methanolic and ethyl acetate extract. The methanolic and ethyl acetate extract showed 56 ± 2.5 and 52 ± 1.53% inhibitions at 20 µg/mL, respectively.

Bone Graft Substitute

Bone defects are a common occurrence in orthopedic and may be caused by various factors such as tumor resection, infection, and trauma. As a result, bone substitutes are currently the preferred treatment (Yeganeh *et al*., 2016). Based on the study of Pinheiro Neto *et al*. (2017) which evaluated gel of lyophilized aqueous extract of *D. ambrosioides* graft against fracture in rabbit, *D. ambrosioides* graft displayed more observable growth of bone callus and better tensile strength of 60.98 N compared to castor oil graft and autogenous bone marrow. The results also noted greater activity of bone alkaline phosphatase and osteocalcin during early fracture healing at 30 days after fracture creation. It was stated that *D. ambrosioides* ability to promote early bone formation involved enhanced collagen deposition and stimulation of osteoblast production that increased tissue resistance. The study indicated that flavonoids might act as a major contributor to bone neoformation.

TOXICOLOGICAL PROPERTIES

D. ambrosioides EO at a concentration above 312.5 µg/mL exhibited cytotoxicity and able to reduce viability of GM 07492-A cells, normal human fibroblasts cells, at IC_{50} of 207.1 ± 4.4 µg/mL (Soares *et al*., 2017). Meanwhile, a study by Buckle (2016) found that *D. ambrosioides* is neurotoxin itself with a narrow therapeutic range; the toxicity was noted to be attributed by camphor and ascaridole content. Through the study conducted by da Silva (2016), the EO of *D. ambrosioides* and some major components of the oil which are carvacrol, caryophyllene oxide, and ascaridole, exerted a toxic effect towards a culture of mouse macrophages. The study believed that the cytotoxic mechanism of action was perceived as inhibition of respiratory function in the mitochondria within the cells. Another study by Monzote *et al*. (2009) found that the toxic effects of caryophyllene oxide and carvacrol content in *D. ambrosioides* may be mediated by complex I inhibition of mitochondrial electron transport chains, while ascaridole toxicity toward oxidative phosphorylation of mammalian mitochondria is dependent on the presence of Ferrous iron (Fe^{2+}).

CONCLUSION

D. ambrosioides, known as Mexican tea, grows wild in Central and South America. Bioactive classes found in this plant are ascaridole, tannins, flavonoids, kaempferol, cardiotonic, anthraquinone, alkaloids, rutin, ethyl acetate, n-heptacosane, n-hentriacontane, n-butanol, n-docosane, aritasone, camphor, *p*-cymene, *p*-cimol, β-pinene, pinocarvone, β-caryophyllene, geraniol, γ-gurjunene, γ-terpineol, α-terpineol, α-terpinene, spinasterol, safrole, thymol, terpinyl-salicylate, terpinyl-acetate, triacontyl-alcohol, quercetin, and chrysin. This plant has been reported to have antibacterial, antiviral, antileishmanial, anticancer, antiprotozoal, antiparasitic, and anthelmintics properties. Moreover, there have been several findings of its other potential pharmacological effects, such as schistosomicidal and nematicidal effects, and also as bone graft substitute, which could be further investigated. On the other hand, there are several toxicological studies of this plant that should be taken into consideration, which include toxicity toward human fibroblasts cells, toxicity toward a culture of mouse macrophages, and its ability to act as a neurotoxin.

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