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A Phytopharmacological Review on Four Antitumor Medicinal Plants Grown in Sudan

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ABSTRACT

Medicinal plants possess immense traditional applications encompassing antibacterial, antifungal, antiviral, antimalarial, antitumor and many. These diverse curative properties attributed to their phytochemicals which can be obtained from different morphological plant parts. In Sudan, medicinal plants are rather diverse species; pertaining with the diverse climate condition. Four plant species namely, *Ambrosia maritima* L., *Ammi visnaga* L., *Aristolochia bracteolata* L. and *Lawsonia inermis* L., are widely held in folkloric medicine for the treatment of vast myriad of diseases including solid mass tumor conditions. This review gives a bird's eye view on the plant species distribution, traditional uses, biological activities and chemical constituents.

Keywords: *Ambrosia maritima* L., *Ammi visnaga* L., *Aristolochia bracteolata* L., *Lawsonia inermis* L., Solid mass tumor, Sudan

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INTRODUCTION

Traditional system of medicine has become a topic of global health importance. This system is still widely held in developing countries as a normative basis for the maintenance of good health and the treatment of vast diseases¹. Cancer is a serious and most vicious human ailment affecting all ages². Though there are various chemotherapeutic manipulations held to cure cancer, the resistance to such therapy as well as its secondary complications negatively impacts its application in clinics³. This had attracted researchers attention to tap the ethnomedicinal knowledge with a hope to deliver new naturally-based molecules. In Sudan, with its unique variable climatic conditions, a huge wealth of flora had been grown wildly or successfully cultivated⁴. These plants species found their way to traditional medicine and the knowledge about their palliative and curative properties to combat diseases had been transmitted from one generation to another⁵. It's worth noting that such medicinal plants are reputed to cure neglected and widely spread infectious diseases, especially resistant bacteria and viral infections, also immunosuppressive disorders and tumor cases were reported to be curable^{6,7}. Thus, it was hoped that this review would shed a light on four medicinal plants species namely, *Ambrosia maritima* L., *Ammi visnaga* L., *Aristolochia bracteolata* L. and *Lawsonia inermis* L., used ethnomedicinally to cure tumor and other various ailments. The review also would reveal previous studies conducted on these species with regard to their biological activities, chromatographic techniques, isolation of active constituents and spectroscopical analysis of the active isolates.

Ambrosia maritima L. (Asteraceae)

Botanical description.



Figure 1: *Ambrosia maritima* L.

Erect branched aromatic herb or undershrub of 1-3feets high. Stems are striate, pilose with whitish hairs. Leaves are petiolate and deeply bipinnately divided up to 4 inches long with a soft and sometimes dense white- pubescent appearance. Flower heads are greenish to yellow, unisexual of 1/6-1/8 inches in diameter. The male heads, with 15-20 flowers at the top, and the female heads,

with 1 apetalous flower at the bottom, are developed in separate heads on the same plant arranged in a pyramidal or corymbose panicle⁸ (Figure.1).

Habitat.

A. maritima, locally known as Damsissa, is a widely distributed weed in northern and central Sudan especially near water catchment and Nile Bank^{6,8}.

Traditional uses.

Traditionally, the decoction of the whole plants is used to cure gastrointestinal disturbance, abdominal pain, kidney inflammation and renal colic, whereas the leaves are used for diabetes and blood pressure. In addition, its curative properties extend to include antimolluscicidal, antimalarial and antitumor activities^{4,9}.

Biological activities and chemical constituents.

The chemotherapeutic property of different *A. maritima*'s extracts was tested on Chinese hamster lung cancer V-79. Both n-hexane and chloroform extracts showed significant activity¹⁰. Chromatographic and spectroscopical analysis of the active extracts revealed the presence of several cytotoxic sesquiterpenes (Figure 2). These sesquiterpenes were later found to have antifungal activity with neoambrosin being the most active one⁹.

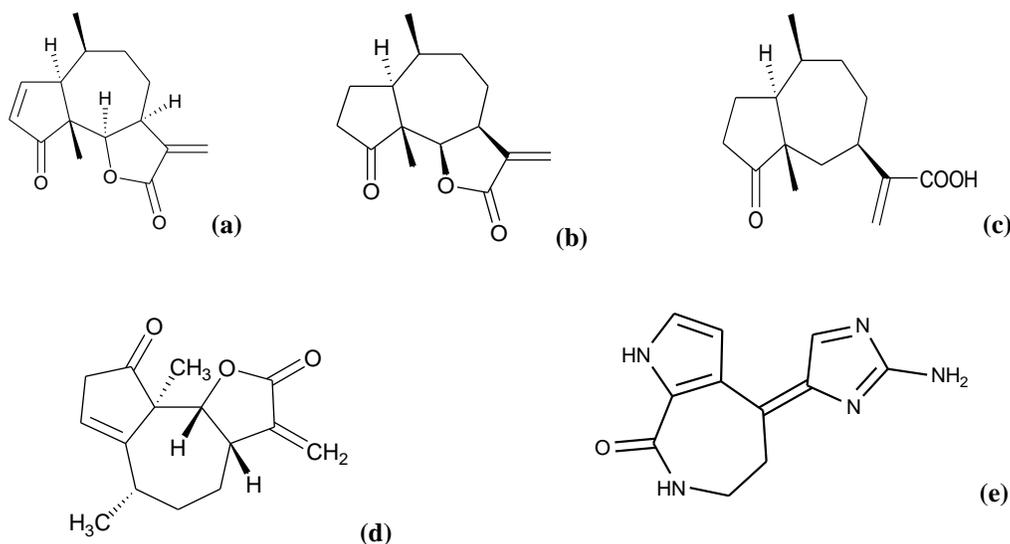


Figure 2: Pseudoguaianolide sesquiterpenes lactones identified in *Ambrosia maritima* L., (a): Ambrosin, (b): Damsin, (c): Damsinic acid, (d): Neoambrosin & (e): Hymenin

Another study was conducted to assess the reputed folkloric use of *A. maritima* in the treatment of kidney inflammation. The plant aqueous extract was tested on two causative strains of kidney inflammation namely, *Streptococcus pyogenes* and *Aspergillus niger*¹¹. Contrary to the literature¹²,

the finding of this study revealed no activity against the tested strains. In continuation with this study, the aqueous extracts were found to display relaxation/contraction phenomena on isolated muscular tissue of rabbit intestine. This finding was considered as a compelling evidence for the ethnomedicinal use of *A. maritima* to relieve colic. On the other hand, the acaricidal activity of *A. maritima*'s leaves was investigated on unfed larvae and adult *Hyalomma anatolicum* ticks using the packet and dipping test, respectively. Both ethanolic and petroleum ether extracts were found to have larvicidal activity¹³. The *A. maritima* petroleum ether extract has been approved to possess chemopreventive activity against ionizing radiation known to cause cellular damage. Chromatographic analysis of the extract revealed the presence of antioxidant phytochemicals namely, sesquiterpene lactones, flavanoids and lignans¹⁴. Recently, the *A. maritima*'s aqueous and ethanolic extracts of the plant showed brine shrimp lethality with LC₅₀ 10.6 and 39.8µg/ml, respectively¹⁵.

***Ammi visnaga* L. (Apiaceae)**

Botanical description.



Figure 3: *Ammi visnaga* L

A. visnaga is an aromatic, annual, erect, glabrous herb about 1- 1.5 m high with branched stem. Leaves are ovate, basal unipinnatisect, upper ones are sessile to sub-sessile. Umbels are mainly terminal rays with very numerous long stiff rays and white flowers. The rays spread in flower and become contracted in fruit. Fruits are ovoid-oblong brownish with violet tinge, laterally compressed with thick glabrous ribs^{12, 16} (Figure 3).

Habitat.

A. visnaga, commonly known as Khella, is native to North Africa¹². In Sudan, the plant is cultivated in northern and central regions⁴.

Traditional uses.

The decoction of khella seeds is reputed to have several curative properties. The decocted seeds are frequently prescribed by local physicians as diuretic and antispasmodic for patients afflicted by uretic stones⁶. The plant is also known to cure vitiligo, psoriasis, cardiovascular disorders, mild obstruction of the respiratory tract in asthma and gastrointestinal cramps¹².

Biological activities and chemical constituents.

A. visnaga's aqueous extract was proved to alleviate kidney stones. This extract showed significant decrease of lactate dehydrogenase (LDH) formation upon renal epithelia cells injured with calcium oxalate¹⁷. Another study attempted to assess the curative effect in vitiligo. Different *A. visnaga*'s extracts were examined for their potential melanin biosynthesis inhibitory activity, to this end, the petroleum ether extract was found to be the most active and five compounds of variable potencies were isolated and identified¹⁸ (Figure 4).

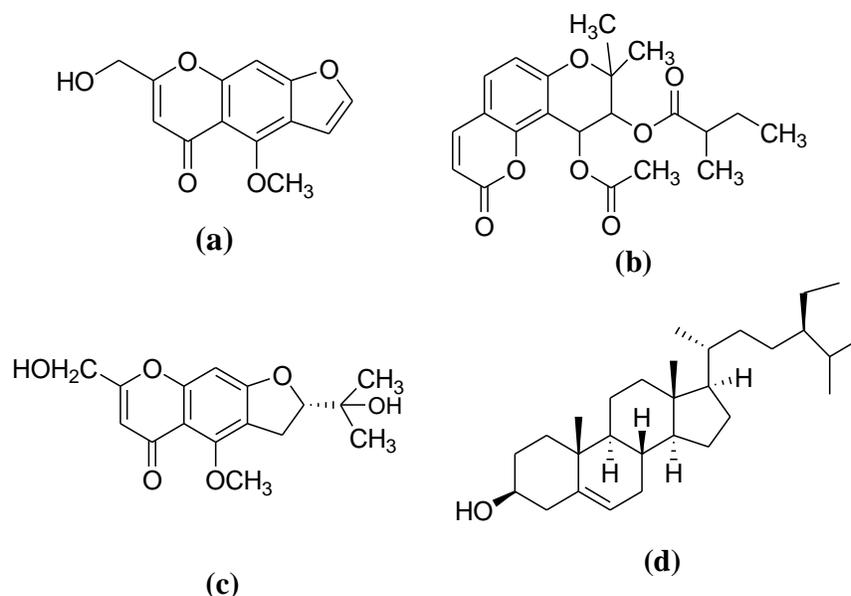


Figure 4: Example of compounds characterized in *Ammi visnaga* L., (a): Khellol, (b): Visnadine, (c): Cimifugin & (d): β -sitosterol

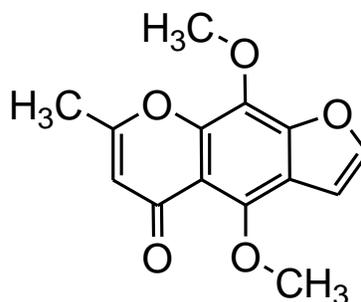


Figure 5: Khellin

These versatile curative properties have encouraged researcher to isolate active constituents from the plant species. Khellin (Figure 5), the most active constituent, is clinically approved to treat coronary insufficiency and angina pectoris¹⁹. In addition, khellin had been found to relax smooth muscle but undesirable side effects precluded its use in the treatment of asthma²⁰. This had encouraged chemists to synthesize khellin analogs as potential bronchodilator with fewer side effects. This eventually led to the discovery of chromolyn⁵ (Figure 6).

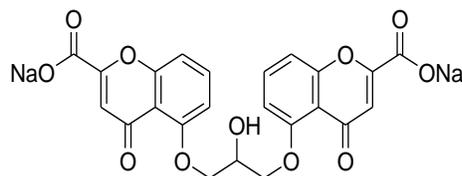


Figure 6: Chromolyn (as sodium chromoglycate)

Phytochemical screening of *A. visnaga* aqueous extract revealed the presence of two flavonoids namely, quercetin and kaempferol (Figure 7). These two natural products are known to have anti-inflammatory, antioxidant and chemopreventive activities ²¹.

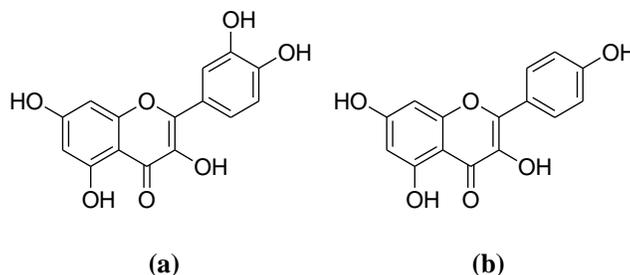
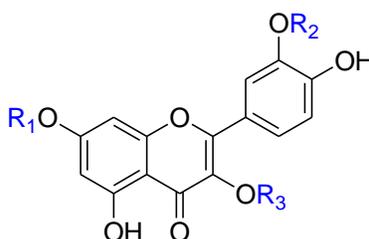


Figure 7: Bioactive flavonoids isolated and identified in *Ammi visnaga* L.

(a): Quercetin & (b): Kaempferol

On the other hand, n-butanol extract revealed unprecedentedly the presence of five flavonoids (Figure 8) along with others. The confirmed antioxidant activity of the n-butanol extract could be viewed as a supportive evidence for the presence of such a class of phytochemicals ²².



Compound name	R ₁	R ₂	R ₃
(a): rhamnetin-3-O-glucosides	CH ₃	H	Glucose
(b): rhamnazin-3-O-glucosides	CH ₃	CH ₃	Glucose
(c): isorhamnetin-7-O-glucoside	Glucose	CH ₃	H
(d): quercetin 3-O- rutinoside	H	H	Rutin
(e): quercetin 7,3,3-O-triglucoside	Glucose	Glucose	Glucose

Figure 8: Five unprecedented flavonoids isolated from *Ammi visnaga* L.

The reputed antimicrobial activity of *A. visnaga* was also proved by different biological studies. Herein, the seeds' aqueous extract showed prominent antibacterial activity against two major oral streptococcus species causing dental caries and periodontal disease ²³. The fruit's aqueous and

ethanolic extracts showed variable activities against six bacterial strains and two yeasts. Although no attempts were done to isolate the active constituents, the researchers postulated the activity to the presence of essential oils, flavonoids, anthocyanins and terpenoids²⁴. This postulation could be supported by a finding that 21 of *A. visnaga*'s essential oils showed a good antibacterial activity against three pathogenic strains namely, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*²⁵. The cytotoxic activity of *A. visnaga* was also cited. In one study, different extracts from the flowering aerial parts were investigated for cytotoxicity against T47D (breast ductal carcinoma) using doxorubicin as standard. The petroleum ether and chloroform extracts showed the most significant cytotoxic activity (IC₅₀ value of 0.40 mg/ml). On the other hand, the least potency (IC₅₀ value of 1.80 mg/ml) was associated with methanol extract. Preliminary phytochemical screening of the most active extracts revealed the presence of coumarins in significant amount, whereas flavonoids were significant in the least potent methanol extract²⁶. Another study explored the inhibitory activity of *A. visnaga*'s volatile oil, extracted by distillation, on two cancer cell lines namely, human pelvic rhabdomyosarcoma (RD) and mouse cell line (L20B). Results showed that the volatile oil caused dose-dependent cytotoxicity²⁷. A third study, conducted in Sudan, revealed that of different *A. visnaga*'s extracts the aqueous and ethanolic ones are the most active in terms of the cytotoxicity to brine shrimps (LC₅₀= 32.6 & 8.1 µg/ml). In continuation with this study, both aqueous and ethanolic extracts showed moderate antioxidant activity¹⁵.

***Aristolochia bracteolata* L. (Aristolochiaceae)**

Botanical description.



Figure 9: *Aristolochia bracteolata* L.

A. bracteolata is an aromatic, deciduous, perennial herb with a smooth erect or twining stem. Leaves are alternate, ovate about 2-3.5 × 1.5- 3 cm, apex rounded, base cordate, margin crenate. Flowers grow in the leaf axils. They are inflated and globose at the base, continuing as a long hairy perianth tube, ending in a tongue-shaped, brightly colored lobe. Fruits are oblong, dehiscent capsule with many endospermic seeds^{28, 29} (Figure 9).

Habitat.

A. bracteolata covers an expansive region in Sudan with a wide distribution in lowland plains and water catchment areas⁶.

Traditional uses.

In Sudan, *A. bracteolata* is traditionally used as a remedy for scorpion and snake bites, pain, tumor, malaria and fever⁶. In African ethnomedicine, it is widely used as anti-inflammatory and anticancer³⁰. The plant is known as “worm killer” due to supposed anthelmintic activity and trypanocidal effect. Furthermore, the *A. bracteolata* possesses potent anti-allergic, antibacterial and antifungal activities³¹.

Biological activities and chemical constituents.

The methanolic extract of the plant's root showed antiplasmodial activity on chloroquine- resistant Dd2 strain of *Plasmodium falciparum*. Interestingly, the extract showed low toxicity on human cells³². Extraction of *A. bracteolata*'s leaves resulted in different antimicrobial fractions. All fractions, except water's one, revealed antibacterial activity with methanol fraction being the most active. Nevertheless, water fraction showed the highest antifungal activity³³. It was implied that the *A. bracteolata*'s chloroform extract had a potent and significant anti-allergic activity elicited by inhibiting nitric oxide (NO) and histamine pathways³⁴. The reputed trypanocidal activity of *A. bracteolata* was also assessed. Different plant extracts were administered to *Trypanosoma evansi* infected rats, where the chloroform extract gave an outstanding parasitic blood clearance (100%) and the methanol extract showed a limited trypanocidal effect³⁵. In an attempt to assess the potential antitumor activity of *A. bracteolata*, several root's extracts were tested against cutaneous melanoma cell line. The petroleum ether extract notably reduced cell survival. Phytochemical investigation of this extract revealed the presence of alkaloids, triterpenes and steroids²⁹. Literature revealed different studies on isolation and characterization of *A. bracteolata*'s bioactive constituents. In this context, isolation of two Aristolochic acid derivatives, with antioxidant activity, from *A. bracteolata* was reported. The methanol extract of the plant powdered leaves and stems were fractionated with different solvent systems. Chromatographic separation followed by structural elucidation of the n-butanol fraction resulted in Aristolochic acids A and D³⁶ (Figure 10). Fractionation of the methanol extract using chloroform/water system followed by chromatographic separation of the chloroform fraction resulted in the isolation of Aristolochic acids A and B (Figure 10). However, the identity of these two acids was inferred solely from their chromatographic profiles³¹. Generally speaking, Aristolochic acids are believed to be the bioactive constituents in *A. bracteolata*³⁷.

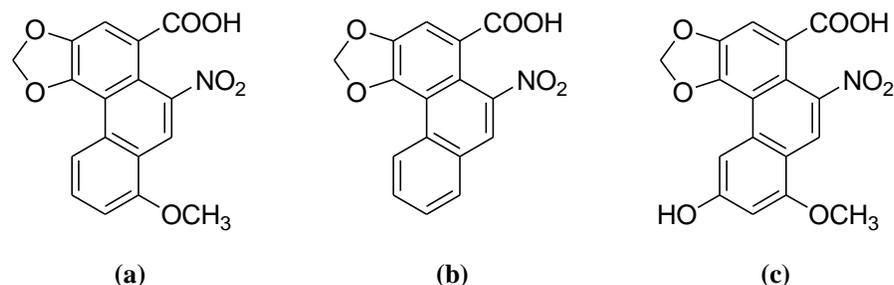


Figure 10: Bioactive Aristolochic acids identified in *Aristolochia bracteolata* (a): Aristolochic acid A, (b): Aristolochic acid B & (c): Aristolochic acid D

Lawsonia inermis L. (Lythraceae)



Figure 11: *Lawsonia inermis* L.

Botanical description.

L. inermis is a perennial, deciduous, branched glabrous or sometime spinescent shrub or small tree with grayish brown bark, attaining a height of 2.4-5 m. The leaves are greenish- brown to brown, opposite, elliptic or oblanceolate, acute at each end, up to about 1.25 inches long and 0.75 inches broad. Flowers are creamy white or rose- colored appearance. The 4 to 8 count Stamens are inserted in pairs on the calyx-tube. Capsules are slightly veined outside about 6 mm in diameter, and supported by the persistent calyx and tipped with the style. Fruits are globose, about 0.25 inches in diameter, with persistent style. Seed capsules are red, globose with numerous tiny pyramidal, brown pitted seeds ^{16, 38}.

Habitat.

L. inermis, commonly known as Henna, is widely distributed in African tropical and subtropical regions. It is cultivated in various parts of Sudan especially the northern and central regions ^{4, 38}.

Traditional uses.

The astringent stem- bark of *L. inermis* is traditionally used for the treatment of jaundice, enlargement of the liver and spleen, and various dermatological disorders ¹⁶. Whereas, the leaves are used as a dyeing material and also used for the treatment of urinary tract infections, fever,

alopecia, headache, diabetes and tumor ⁶. Furthermore, Henna, like other Sudanese medicinal plants, is known to have immunomodulatory properties ^{4,39}.

Biological activities and chemical constituents.

To assess immunomodulatory properties, the leaves' methanolic extract of *L. inermis* was subjected to an *in vitro* immunoassay. Bioassay-guided fractionation resulted in an unprecedented isolation of *p*-coumaric acid, 2-methoxy-3-methyl-1,4-naphthoquinone and apiin from chloroform and ethyl acetate fractions ³⁹ (Figure 12).

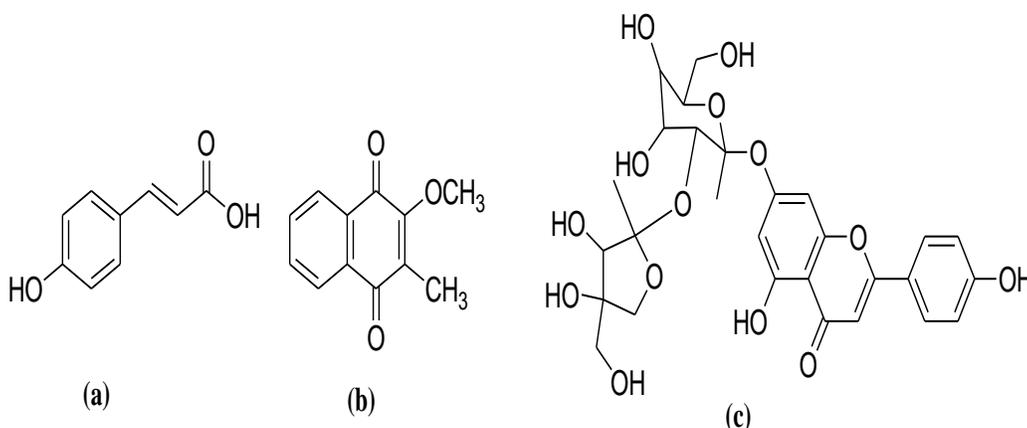


Figure 12: Immunomodulatory compounds isolated from *Lawsonia inermis*, (a): *p*-coumaric acid, (b): 2-methoxy-3-methyl-1,4 naphthoquinone & (c): Apiin

The methanolic extract of *L. inermis* showed significant *in vitro* hypoglycemic activity using glucose oxidase method ⁴⁰. Shortly afterwards, the ethanolic leaves' extract proved to have an *in vivo* hypoglycemic activity in diabetic mice ⁴¹. Very recently, the ethanolic seeds' extract has been reported to control blood glucose in diabetic mice without any effect on normal blood glucose level. Needless to say, the extract showed no sign of acute toxicity upon renal, liver, and hematological assessments ⁴². The chloroform extract of *L. inermis* displayed no cytotoxic effect on colon cancer cell line (Caco-2). Nonetheless, the extract showed marked cytotoxicity towards human liver cancer cell line (HepG2) and hormone-dependent breast cancer cell line (NCF-7) ⁴³. The *L. inermis* aqueous and methanolic extracts have been approved to possess cyto-protective activity against Cr(VI)-induced oxidative cellular damage. HPLC analysis of both extracts identified some phenolic compounds to which the cytoprotection was attributed ⁴⁴. Bioassay-guided fractionation of *L. inermis* stems' methanolic extract resulted in isolation of 31 anti-inflammatory compounds of which lawsochylin A and lawsonaphthoate A (Figure 13) were the most potent ⁴⁵.

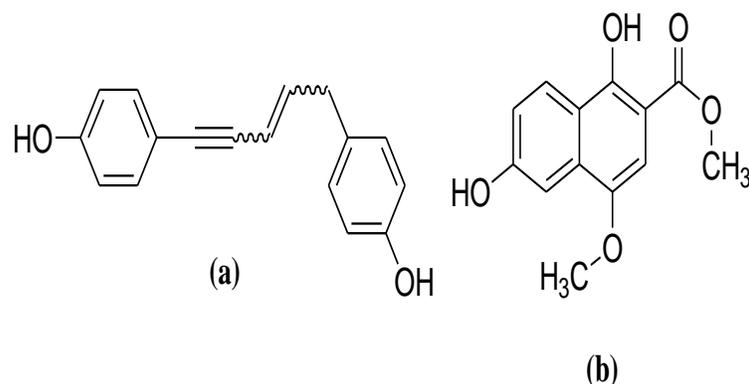


Figure 13: Anti-inflammatory compounds isolated from *Lawsonia inermis*, (a): lawsochylin A & (b): lawsonaphthoate A

CONCLUSION

In conclusion, the present review on the four selected plant species, *Ambrosia maritima* L., *Ammi visnaga* L., *Aristolochia bracteolata* L. and *Lawsonia inermis* L., endorses with scientific manipulations their ethnomedicinal usage. Furthermore, the inherited information pertaining with their antitumor activity would, hopefully, provide an avenue to explore new antitumor leads.

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