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Review Article

Toxicological Review of Anticancer Plants Used in Traditional Medicine in Morocco

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Abstract: In Morocco, traditional medicine utilizes many toxic plants for cancer treatment, despite a lack of scientific evidence supporting their effectiveness. Further research may be able to explore and discover the potential therapeutic effects of these plants' bioactive molecules with antioxidant and anticancer properties. Based on our review, we have determined that the 13 plants under examination possess various pharmacological and biological activities due to their diverse phytochemical composition. Despite their toxicity, these plants have a history of traditional use in Morocco for treating multiple diseases. Further research, including preclinical and clinical trials, should be conducted to investigate the potential therapeutic benefits of these plants. Moroccan cuisine commonly incorporates gruels, herbal drinks, and spicy beverages, which possess significant health benefits, including chemo-preventive properties and natural inhibitors against certain infections.

These properties may aid in reducing the incidence of cancer and potentially have therapeutic effects in various human pathologies when consumed in appropriate amounts and in combination with a healthy lifestyle.

Keywords: Toxic plants; anticancer activity; traditional medicine, Morocco.

1. Introduction

Toxic and poisonous plants are characterized by their ability to accumulate one or more toxic chemical compounds. These compounds may include alkaloids, terpenes, phenolic compounds, and proteins. These toxic substances can be present in specific parts of the plant or the entire organism[1].

From a toxicological perspective, the toxins mentioned above have the potential to impact the central nervous systems of both humans and animals, resulting in chronic, acute, and occasionally fatal intoxications. Alkaloids, which constitute approximately 45–47% of the total toxins found in most plant families, is considered to be the most prevalent toxic compound. Terpenes, representing 27–31% of the toxins, are the second most prevalent. Phenolic compounds, accounting for 10–12%, are the third most prevalent. The remaining toxins, including proteins, amino acid derivatives, thioglucosides, oxalic acid, and nitrates, constitute 15–17%[2].

Toxins can be present in various plant parts or the entire organism. A study of 13 organs of plants revealed that the whole plant, seeds, leaves, latex, and fruits could accumulate large quantities of toxins. The percentage of toxicity among these different parts indicates that the entire plant accounts for 27.45% of cases. Seeds and leaves occupy the second position with respective percentages of 13.7% and 15%. Latex and fruits show rates of 11.7% and 11%. The remaining toxic parts, including the root, essential oil, rhizome, bulb, flower, pollen, stem, and resin, are represented by a cumulative rate of 24.83%. Secondary metabolism in plants refers to a series of biochemical reactions or transformations that occur within the plant and can contribute to the accumulation of toxins[2,3].

Medicinal plants have been found to possess various biological properties with potential therapeutic effects against diseases such as microbial infections, urinary lithiasis, cancer, and other oxidative stress-related diseases[4–6].

The pharmacological properties of medicinal plants, such as cancer chemoprevention and cytotoxic effects, are believed to be attributed to various phytochemicals, including

flavonoids, alkaloids, and terpenes in the plant species[7,8]. Therefore, it is vital to screen some commonly used toxic plants in Morocco to identify and isolate the bioactive molecules that may be responsible for their traditionally reported therapeutic effects[9–11].

This review aims to highlight toxic plants with the reported anticancer activity used in Morocco's traditional medicine to treat various diseases. To achieve this objective, 13 toxic plants with potential anticancer properties were selected from the traditional Moroccan pharmacopeia and investigated for their use in diverse therapeutic pathways and the treatment of various pathologies in Morocco. A summary of the phytochemical composition, anticancer activity, toxicological properties, and the traditional use of the included plants is presented in Supplementary Table S1.

2. The Toxic Anticancer Plants

2.1. Geographical Location of Aristolochia Longa (A. Longa)

A. Longa, or turmeric, is a medicinal plant from the Aristolochiaceae family. It is widely distributed in Asia, Africa, and North and South America[12]. This plant is commonly found in tropical, subtropical, and Mediterranean regions[13].

2.2. Phytochemical Composition

According to a study by M. Dhouiouia *et al*., the essential oil of *A. Longa* is characterized by a high content of oxygenated sesquiterpenes (50.2–81.1%), followed by oxygenated monoterpenes (5.9–28.0%), sesquiterpene hydrocarbons (0.7–18.4%), and monoterpene hydrocarbons (0.0–0.8%). Regardless of the season, the significant component of the essential oil was found to be maaliol. Reciprocal trends were observed for aromadendrene and its oxygenated derivatives[14]. Another study by B. Benarba *et al*. reported the presence of polyphenols, flavonoids, tannins, heterosides, carbohydrates, and saponins but did not detect the presence of alkaloids and coumarins[15].

2.3. Anticancer Activity

A. Longa has been shown to exert antitumor activity through its immunostimulatory effects, induction of an inflammatory response, and high cytotoxicity, resulting in the development of tissue necrosis. According to a study by G. Benzakour *et al*., treatment with *A. Longa* extract was found to amplify 4-nitroquinoline1-oxide (4NQO)-induced hyperplasia compared to controls. Many mononuclear cells were observed in filtrates, lymphoid follicles, and lymph nodes in animals treated with *A. Longa*. Additionally, many

eosinophils were observed in the different tissues examined. The inflammatory reaction and cytotoxicity mechanisms can be explained by the release of reactive oxygen species (ROS) by activated eosinophils, which then leads to the catalyzation of the reduction of oxygen to superoxide by Nicotinamide Adenine Dinucleotide Phosphate oxidase (NADPH)[16].

A study by B. Benarba *et al*. investigated the effects of an aqueous extract of *A. Longa* roots on cell viability in vitro by incubating human breast epithelial cell line HBL100 and MDA-MB-231 breast cancer cells with different concentrations of the aqueous extract. Cell viability was determined after 48h and 72h using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium (MTT) Bromide assay. The results showed that both cell lines were inhibited dose-dependent by the aqueous extract of *A. Longa* after 72h of incubation. The concentration of 500µg/ml of aqueous extract of *A. Longa* induced cell death in 91.99% and 96.97% of HBL 100 and MDA-MB-231 cells, respectively[15].

2.4. Toxicological Properties

A study by G. Benzakour *et al*. found that the aqueous extract of *A. Longa L*. at a dose of 1.25 g/kg did not produce toxic effects in mice and did not induce histopathological changes in kidney, liver, and intestine tissues. However, at a dose of 2.5 g/kg, it produced toxic effects in mice after six weeks of treatment by oral gavage, such as atypical locomotion, anorexia, asthenia, ataxia, diarrhea, and increased urination. These symptoms were observed immediately after oral administration of the extract and persisted until the end of the experiment[16].

Another study by Cherif H.S *et al*. found subacute oral toxicity of the aqueous extract of *A. Longa L*. (1.5 g/kg) resulted in a slight decrease in body weight and diarrhea in treated mice. However, more severe toxic effects, such as diarrhea, fatigue, and weight loss, were observed in the 2.5 g/kg and 3.5 g/kg dose groups[17].

2.5. Traditional Use

The species *A. Longa*, known as "Barraztam" locally, is frequently used in Moroccan traditional medicine. Traditional healers often prepare a small amount of rhizome powder mixed with honey or salted butter to treat upper respiratory infections and abdominal pain[18]. Currently, the *A. Longa* roots are commonly used to treat digestive disorders, constipation, and aortic palpitations (bûmezwi) in traditional medicine. It is also used in Marrakech to treat skin conditions, particularly mycosis[19]. The species *A. Longa*, known as "Barraztam" locally, is frequently used in Moroccan traditional medicine. Traditional

healers often prepare a small amount of rhizome powder mixed with honey or salted butter to treat upper respiratory infections and abdominal pain[18]. Currently, the *A. Longa* roots are commonly used to treat digestive disorders, constipation, and aortic palpitations (bûmezwi) in traditional medicine. It is also used in Marrakech to treat skin conditions, particularly mycosis[19].

3. *Artemisia Herba-alba (A. Herba-alba)*

3.1. Geographical Location

A. Herba-alba, also known as *Artemisia herba-alba*, is a species of the Asteraceae family native to North Africa, ranging from Morocco to Egypt. The plant is a shrubby undergrowth found in various habitats, including plateaus, steppe areas, and the Sahara. *A. Herba-alba* typically forms clumps of 0.3 to 0.8 meters and is a salty and whitish appearance. Its leaves are finely divided and give off a strong aroma. The yellow flowers are small[20,21].

3.2. Phytochemical Composition

A. Herba-alba contains diverse secondary metabolites, the most prominent being sesquiterpene lactones[22] ; esquiterpene lactones are a prevalent class of natural products found in Artemisia species and are considered to be responsible for the medicinal and pharmaceutical importance of these plants. Different structural types of sesquiterpene lactones have been identified in the aerial parts of *A. Herba alba*[23] (Figure 1).

A. Herba-alba has been found to contain a wide range of flavonoids, which vary in structure from common flavones and flavonol glycosides to highly methylated flavonoids. Some studies on *A. Herba-alba* leaves collected from Sinai (Egypt) have resulted in the isolation and identification of a total of eight O- and C-glycoside flavonoids[24,25].

Additionally, phenolic compounds and waxes of chlorogenic acid have also been observed in *A. Herba-alba*. A chemical study of 49 Moroccan drugs was performed by ESR (electron spin resonance) spectroscopy, which identified the presence of these compounds in the plant species[26].

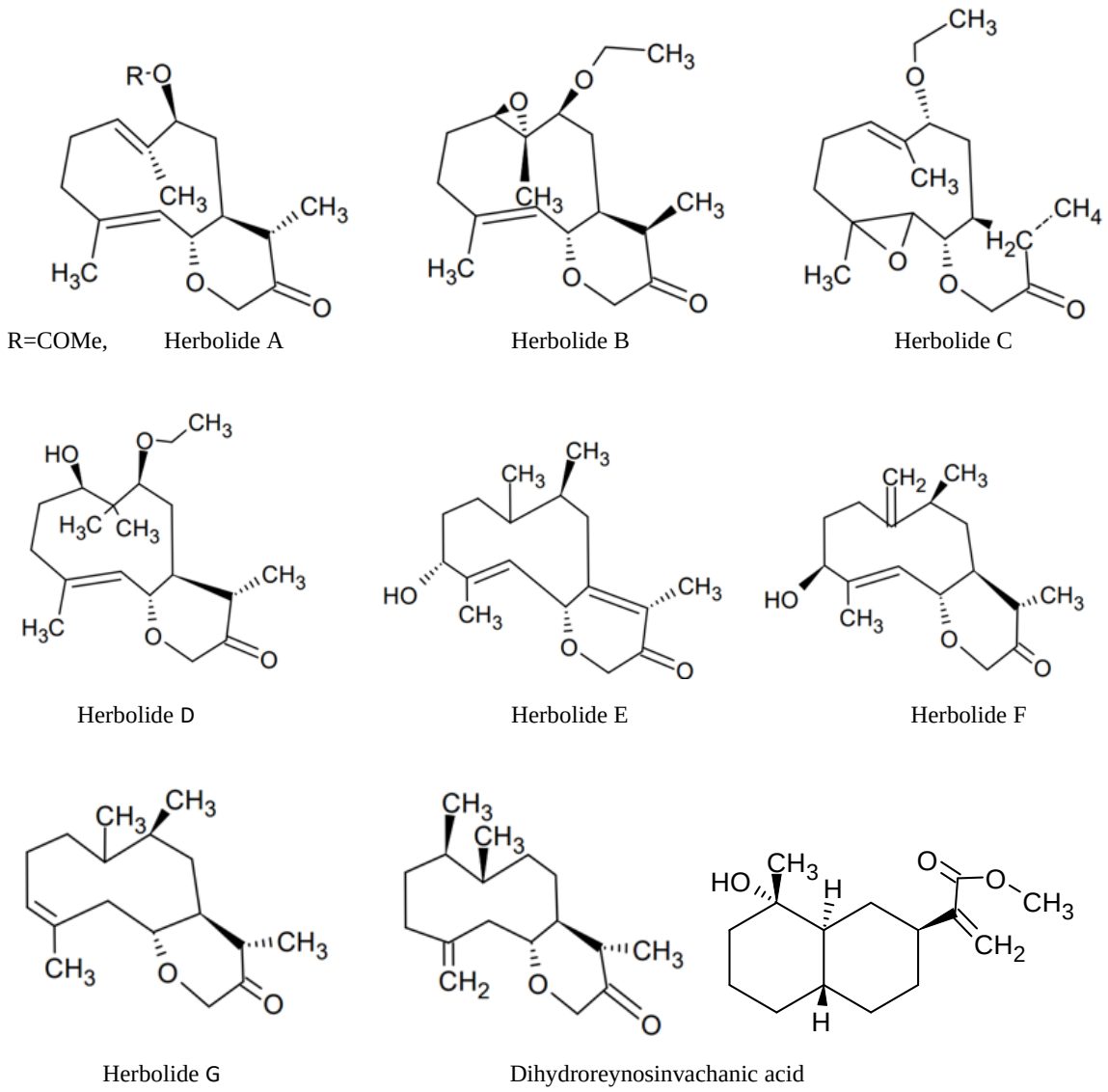


Figure 1. Some Sesquiterpene lactones from *A. herba-alba.*

An investigation of the antiulcerogenic properties of *A. Herba-alba* led to the isolation of eight polyphenols and their related constituents. These include chlorogenic acid, 4,5-O-dicaffeoylquinic acid, isofraxidine 7-O-β-D-glucopyranoside, 4-O-β-D-glucopyranosylcaffeic acid, rutin, schaftoside, isoschaftoside, and vicenin-2. Additionally, a study of the components of the wax of *A. Herba-alba*, obtained by extracting the dry plant with ether, revealed that it contains 32.1% saturated acids, 23.2% hydrocarbons, 27.1% esters, and 16.96% saturated alcohols (Figure 2)[27].

The essential oil of *A. Herba-alba* mainly comprises oxygenated monoterpenoids, such as 1,8-cineole, chrysanthenone, chrysanthenol (and its acetate), α/β-thujones, and camphor[28].

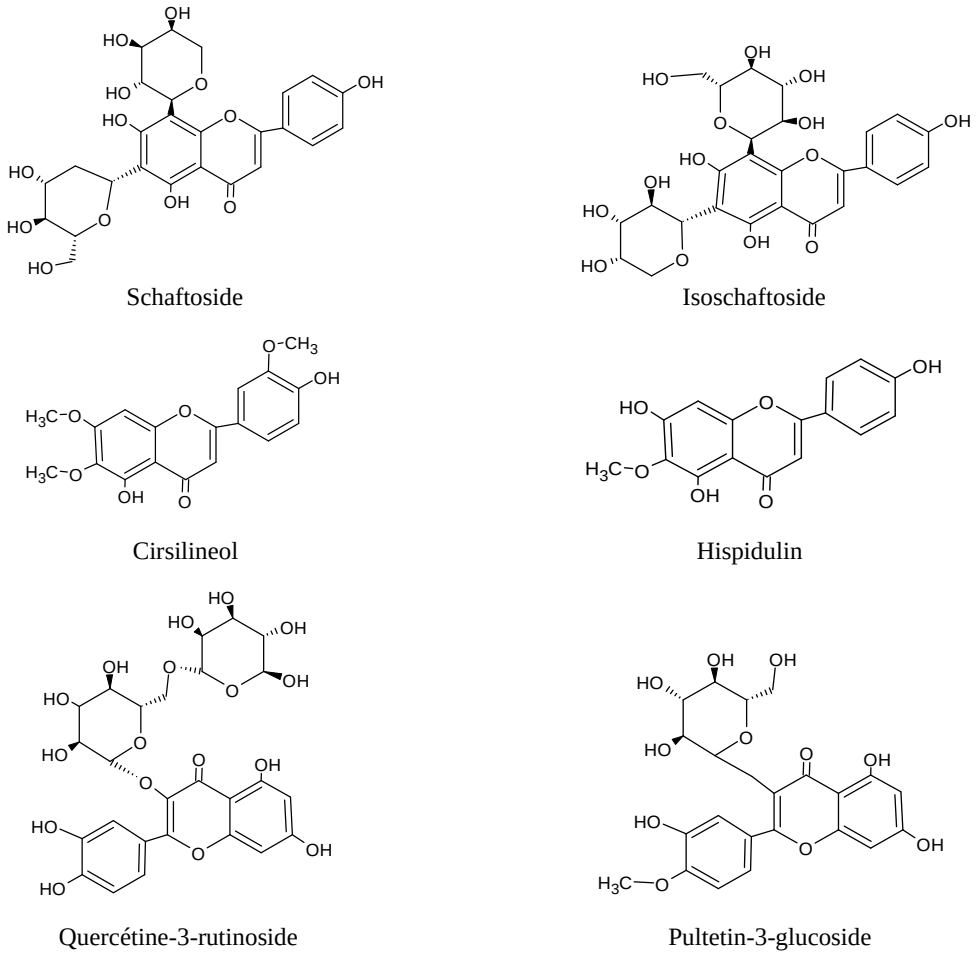


Figure 2. Some Flavonoids of *Artemisia herba-alba*.

3.3. Anticancer Activity

An evaluation of the cytotoxicity of the hydroalcoholic extract (methanol/water; 3/1) of *A. Herba-alba* was conducted against several cell types, including RT112 cells, Hep2 cells, K562 cells, and PBMC (peripheral blood mononuclear cells) cultured with PHA (phytohemagglutinin). The results indicated that all extracts exhibited dose-dependent cytotoxic activity, suggesting that *A. Herba-alba* extracts target carcinoma cell lines and induce their destruction. This type of response has been previously observed for the natural phenolic compound thymol, which induces dose-dependent cytotoxicity on HL-60 cells. These findings highlight the potential of *A. Herba-alba* as a source of new chemo-preventive agents against cancer progression[29].

3.4. Toxicological Properties

A study on the effects of *A. Herba-alba* on maternal organ weights and embryo weights in female rats showed a slight but non-significant reduction in body and uterine

weights. However, compared to controls, a statistically significant decrease in the relative weight of the ovary and embryo was observed in the treated group[30].

3.5. Traditional Use

The traditional uses of *A. Herba-alba* in Moroccan medicine includes being prescribed as a venom-repellent, emmenagogue, stomachic, intestinal antiseptic, tonic, depurative, cholagogue, and antidiabetic[31].

4. *Calotropis Procera (C. Procera)*

4.1. Geographical Location

C. Procera is a species of flowering plant in the Apocynaceae family, native to North Africa, tropical Africa, Western Asia, South Asia, and Indochina. This species, known as Sahara-Sindiana, is frequently found in the central and southern Sahara and extends to Moroccan Western Sahara[32].

4.2. Phytochemical Composition

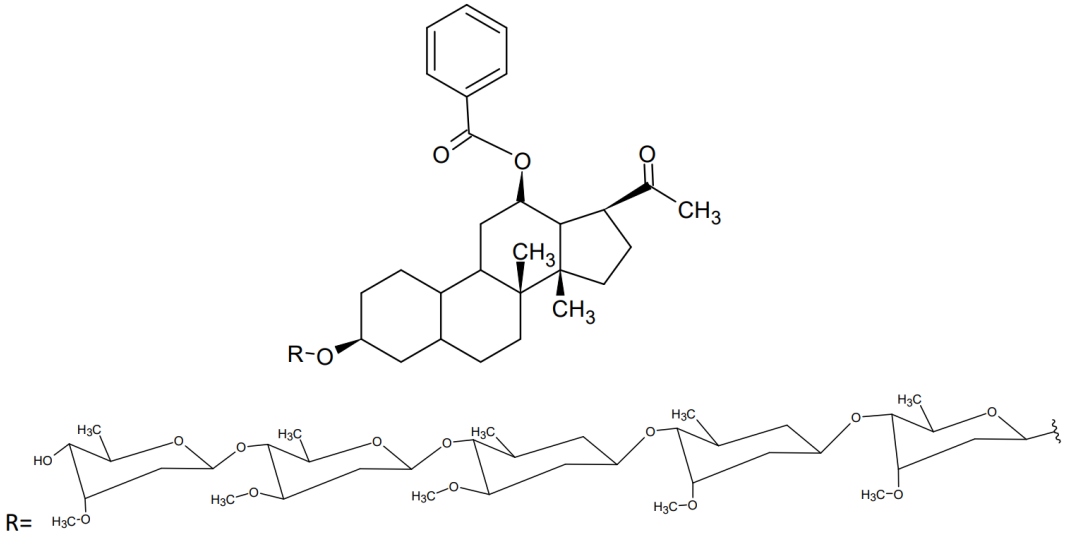
Researchers have reported that *C. Procera* has various bioactive compounds in the aerial parts of the plant, including 3-O-rutinoside, kaempferol, isorhamnetin, and flavonoid glycoside 5-hydroxy-3,7-dimethoxyflavone-40-Ob-glucopyranoside. The latex of *C. Procera* is particularly rich in bioactive compounds such as cardenolides, proteolytic enzymes, alkaloids, and carbohydrates[33].

C. Procera contains cardioactive glycosides, calactin, calotropain, calotropagenin, proceroside, syriogenin, calotoxin, uscharin, uzarigenin, uscharidin, voruscharin, tannins, flavonoids, sterols, and triterpenes[34]. Other compounds found include benzoylisolineolon and benzoyllineolone[35], procesterol, a steroidal hydroxy ketone[36], flavonol glycosides[37], organic carbonate with stigmasterol and sitosterol[38].

4.3. Anticancer Activity

Ibrahim *et al*. conducted a study to evaluate the n-BuOH fraction of the root bark of *C. Procera* against three cancer cell lines. Seven novel oxypregnane oligoglycosides, calotroposides H-N (1–7; Figure 3), were isolated, and their structures were determined using spectroscopic data. The in vitro growth inhibitory activity of these compounds was evaluated against A549 NSCLC (Deutsche Sammlung von Mikroorganismen und Zellkulturen, DSMZ; code ACC107), U373 GBM (European Collection of Cell Culture,

ECACC; code 89081403), and PC-3 (DSMZ; code ACC465) cell lines using the MTT colorimetric assay. The study showed that compounds 4 and 6 were the most active against these cancer cell lines. A significant difference in growth inhibitory activity was observed among the three cell lines tested[39].



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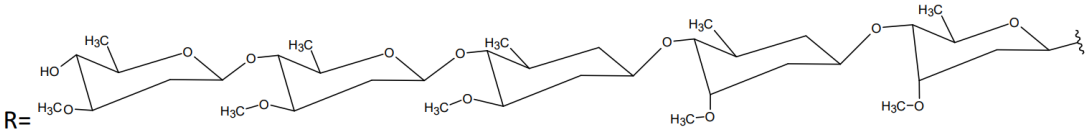

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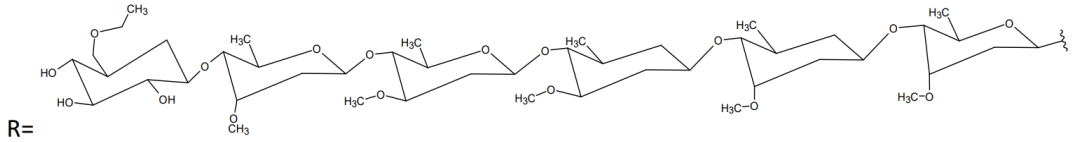

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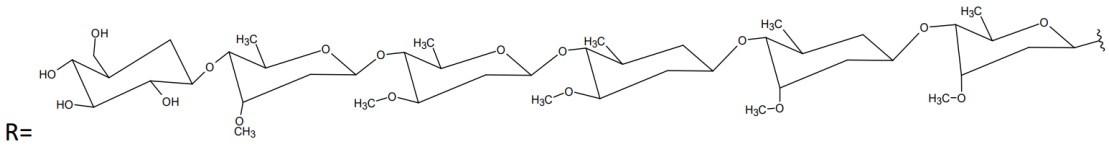

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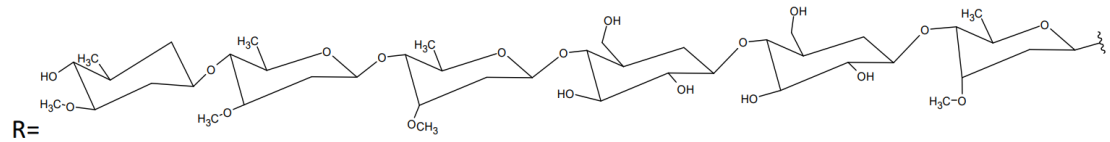

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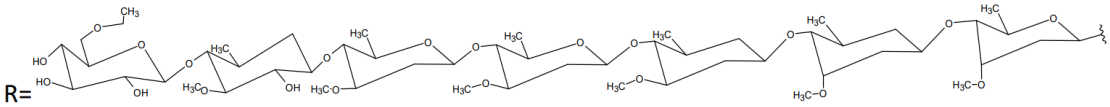

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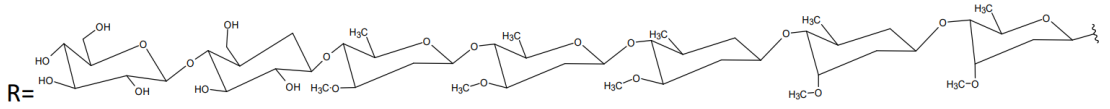

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Figure 3. Structures of the isolated compounds 1–7.

4.4. Toxicological Properties

In a subacute toxicity study, the administration of *C. Procera* extract in animal models did not result in mortality or significant behavioral changes over 28 days. However, a slight decrease in body weight and morphological changes in some organs were observed in treated groups. These changes could result from fat accumulation or decreased appetite rather than toxicity from the extract. Phytochemical compounds present in *C. Procera*, such as cardenolides and alkaloids, have been known to have toxic effects. Their accumulation over time may affect thrombopoiesis and adversely affect the spleen and liver function, as reported in previous studies[40,41,42].

4.5. Traditional Use

In Morocco, the powder of dried leaves from *C. Procera* is traditionally used as a vermifuge in low doses. However, it has a strong purgative effect when consumed in larger quantities, such as a small amount of latex mixed with semolina porridge. It is typically only used by individuals of solid constitution. The emetic and cathartic properties of latex, known to nomadic communities, are also utilized in treating acute intoxications. The latex and decoction of the bark are also commonly used in veterinary medicine to treat leprosy and scabies[43].

5. *Cannabis Sativa* (*C. Sativa*)

5.1. Geographical Location

C. sativa, commonly known as cannabis, is a flowering plant species belonging to the Cannabaceae family, native to Central Asia. It is widely distributed in Egypt and Western Asia and has been introduced in Europe, South America, and North America. In Morocco, *C. sativa* is commonly cultivated in mountainous regions such as the Rif, on forest soils rich in humus, and in areas with access to water points. Cultivation of *C. sativa* in Morocco requires significant irrigation and is commonly found in regions such as Alhucema, Tetouan, Chaouen, Taounate, Larache, Sefrou, Fez, Meknes, Essaouira and Ait Ourirn[44].

5.2. Phytochemical Composition

Cannabis (Cannabis sativa, or hemp) has been used for multiple purposes (medicinal, recreational, seed oil, industrial fiber, etc.) for thousands of years. Its psychoactive and physiologically active constituents, known as cannabinoids, are found in the flowers (and to a *Cannabis sativa*, commonly known as hemp, has a long history of use for various purposes, including medicinal, recreational, and industrial applications. The plant's active compounds, known as cannabinoids, are primarily found in the flowers and, to a lesser extent, in the leaves, stems, and seeds. The most well-known cannabinoid is delta-9-tetrahydrocannabinol (Δ9-THC), responsible for the plant's psychoactive effects. Other non-psychoactive cannabinoids, such as cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) have also been found to have medicinal properties. Over 545 compounds have been identified in the cannabis plant, with research suggesting potential medical applications for treating various diseases. The first compound isolated from the plant was cannabinol in 1942, followed by cannabidiol in 1963, and delta-9-tetrahydrocannabinol in 1964 by Raphael Mechoulam and Gaoni[45,46,47,48].

5.3. Anticancer Activity

Cannabis (Cannabis sativa, or hemp) has been used for various purposes, including medicinal, recreational, seed oil, and industrial fiber, for thousands of years. Its active compounds, known as cannabinoids, are primarily found in the plant's flowers and, to a lesser extent, in the leaves, stems, and seeds. Δ9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid, while cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) are non-psychoactive compounds with medicinal properties. The

cannabis plant also contains other natural compounds, with 545 constituents reported to date.

Endocannabinoid receptors, CB1 and CB2, are expressed in various tissues and breast cancer cells[39]. MCF-7 (Michigan Cancer Foundation-7) breast cancer cells are highly metastatic estrogen and progesterone receptor-positive cells that express the CB1 receptor, similar to other breast cancer cells and tissues. Cannabis-based medicines, as modulators of corticospinal excitability, may provide new therapy options for managing cancer pain, not only for those who do not respond to standard therapies, but also for patients who prefer to try cannabis as a first-line treatment[49,50,51].

The potential of *Cannabis sativa (C. sativa)* extracts as anti-cancer agents were evaluated in a study using MCF-7 breast cancer cells. The cells were exposed to dichloromethane (DCM) extracts of *C. sativa* samples for 24 and 48 hours. The results indicated that at 24 hours, the exposure to the DCM extracts showed no significant cytotoxicity in the MCF-7 cells. However, all eight extracts from the *C. sativa* samples showed IC_{50} values of 65 to 100 μg/ml at 48 hours of exposure. This suggests that these extracts may have moderate cytotoxicity as per the criteria set by the National Cancer Institute (NCI). Further study is needed to determine the potential of *C. sativa* extracts as anti-cancer agents and understand the mechanisms of action via regulation of CB1 receptors and VEGF expression in MCF-7 cells[52].

5.4. Toxicological Properties

The primary psychoactive component of cannabis, tetrahydrocannabinol (THC), interacts with the body's endocannabinoid system, composed of cellular receptors, endogenous ligands, and various intracellular messengers that are involved in the synthesis, degradation, control, and regulation of this system. The endocannabinoid system plays a significant role in modulating the function of the nervous system. According to the scientific literature, the maximum daily dose of THC for humans is around 1mg of THC from 24.5g of cannabis[53]. Cannabis (*Cannabis sativa*), commonly known as marijuana, contains various psychoactive and physiologically active compounds called cannabinoids. The primary psychoactive component of cannabis, tetrahydrocannabinol (THC), interacts with the body's endocannabinoid system, which regulates various physiological processes. However, accidental ingestion of cannabis, particularly by children, can lead to severe psychomotor disturbances, such as ataxia, drowsiness, and coma[54].

Additionally, cannabis sold in the illegal market may contain potentially toxic

contaminants, such as fecal bacteria, yeast, pesticide residues, and heavy metals, which can lead to respiratory and neurological diseases when inhaled. Inhalation of bacteria and yeast can also induce asthma attacks[55,56]. Furthermore, some sellers may cut cannabis with other products to increase profit and appeal, potentially leading to dangerous or misleading results[57].

5.5. Traditional Use

In Morocco, *C. Sativa* (Indian hemp) has been traditionally used as a sedative for severe pain. In the past, it was also commonly used by surgeons as a sedative and anesthetic before surgical procedures, often in combination with other plants such as hemp and mandrake[50].

6. *Chenopodium ambrosioides (C. ambrosioides)*

6.1. Geographical Location

Dysphania ambrosioides, also known as wormwood, Jesuit tea, or Mexican tea, is a short-lived annual or perennial herb native to Central and South America and Mexico. In addition to its native range, it is cultivated in temperate and warm subtropical regions of Europe and the United States, such as Missouri, New England, and the Eastern United States. This plant is also widely distributed in Africa, particularly Morocco, Nigeria, Senegal, Ghana, and Cameroon[58,59].

6.2. Phytochemical Composition

The essential oil of *Dysphania ambrosioides*, also known as wormwood, was analyzed by Adebayo *et al*. and found to be primarily composed of monoterpene hydrocarbons (76.8%), with the most abundant compounds being α-Terpinene (53.4%) and p-cymene (21.1%). Additionally, trace amounts of other compounds were identified, including limonene (1.4%), γ-terpinene (0.8%), and carvacrol (1.1%). The presence of carvacrol, an anthelmintic compound, is noteworthy in the context of the traditional use of wormwood for treating parasitic infections.

The major phytochemical compounds in *Dysphania ambrosioides*, known as wormwood, are flavonoids and phenolic acids. Flavonoids, specifically quercetin and kaempferol derivatives, constitute the majority of the compounds present in the plant, with quercetin 3-O-rutinoside and kaempferol dirhamnoside-O-pentoside being the most abundant. Additionally, phenolic acids, such as trans-p-coumaric acid, are present in the

plant. The plant also contains various fatty acids, with polyunsaturated fatty acids, alpha-linolenic and linoleic acids, being the most prevalent. These compounds have been previously shown to have potential health benefits, particularly in preventing cancerous diseases[59].

6.3. Anticancer Activity

The cytotoxic potential of *C. ambrosioides* was evaluated by testing its essential oil, ethanolic extract, and fractions prepared by liquid/liquid fractionation with dichloromethane, ethyl acetate, and butanol in tumor cell lines (K562 (myeloid leukemia), NALM6 B15 (acute B lymphocytic leukemia), and RAJI (Burkitt's lymphoma)). The results showed that the essential oil displayed significant cytotoxicity against RAJI cells (IC_{50} = 1.0 g/ml), and the dichloromethane fraction and ethanol extract demonstrated cytotoxicity against K562 cells (IC_{50} = 34.0 g/ml and 47.0 g/ml respectively)[60].

The activity of the essential oil is thought to be attributed to the high concentration of ascaridol, as the other primary compound, p-cymene, has been shown to have low cytotoxic activity. The study concluded that ascaridol is responsible for the cytotoxicity observed in the analyzed cells, and that the essential oil and fractions of *C. ambrosioides* possess cytotoxic potential[61].

6.4. Toxicological Properties

Chronic toxicity studies in albino rats have shown that high doses of *C. ambrosioides*, ranging from 12.31 to 31.89 g/kg, administered over 42 days, can lead to pathological symptoms such as metaplastic alterations in the mucosal surface of the stomach, congestion of the lungs, and necrosis of the kidney tubules[62]. An overdose of *C. ambrosioides* oil has resulted in fatalities in humans and rats[63].

The toxic effects are attributed to ascaridol, a compound isolated from the *C. ambrosioides* oil, which has various biological activities but also exhibits toxic or genotoxic effects[63].

6.5. Traditional Use

The seeds of *Dysphania ambrosioides*, also known as *C. ambrosioides*, are traditionally used as a vermifuge in the Marrakech region of Morocco. However, the whole plant is more commonly used as an infusion or fresh juice to treat gastrointestinal ailments, typhoid, and dysentery in both adults and children and promote lactation. In the Sale region

of Morocco, the fresh plant of *D. ambrosioides* is applied topically to treat oral abscesses, ulcerations, and purulent wounds[64].

7. *Conium Maculatum* (*C. Maculatum*)

7.1. Geographical Location

C. maculatum, a member of the Apiaceae family, is widely recognized as one of the most toxic plant species. It is native to Europe, Asia, North Africa, North America, Australia, and New Zealand[65]. Additionally, it is present in nearly all South American countries[66]. Despite its toxicity, it is not considered a significant problem in animal production in Brazil[67]. However, it is well known in Argentina as a toxic plant, with reports of acute and teratogenic toxicity[68]. This species is widespread in the country but is particularly prevalent in the Pampa region, which is also an area of high animal production. In Morocco, it is commonly found in humid areas near buildings[69].

7.2. Phytochemical Composition

Chemical analysis of *Cicuta maculatum* (hemlock) has revealed that all plant tissues contain alkaloids, with the fruits having the highest concentration at up to 1% (w/w). The amount and ratio of alkaloids present can vary depending on the variety of the plant, the ecological conditions, and the stage of phenological development. Eight known piperidine alkaloids are present in hemlock, including coniine, N-methylconiine, conhydrin, pseudo-conhydrine, and gamma-coniceine. Coniine is considered to be eight times more toxic than γ-coniceine . In addition to alkaloids, *C. maculatum* contains flavonoids, coumarins, polyacetylenes, vitamins, essential oils, and non-volatile oils[70].

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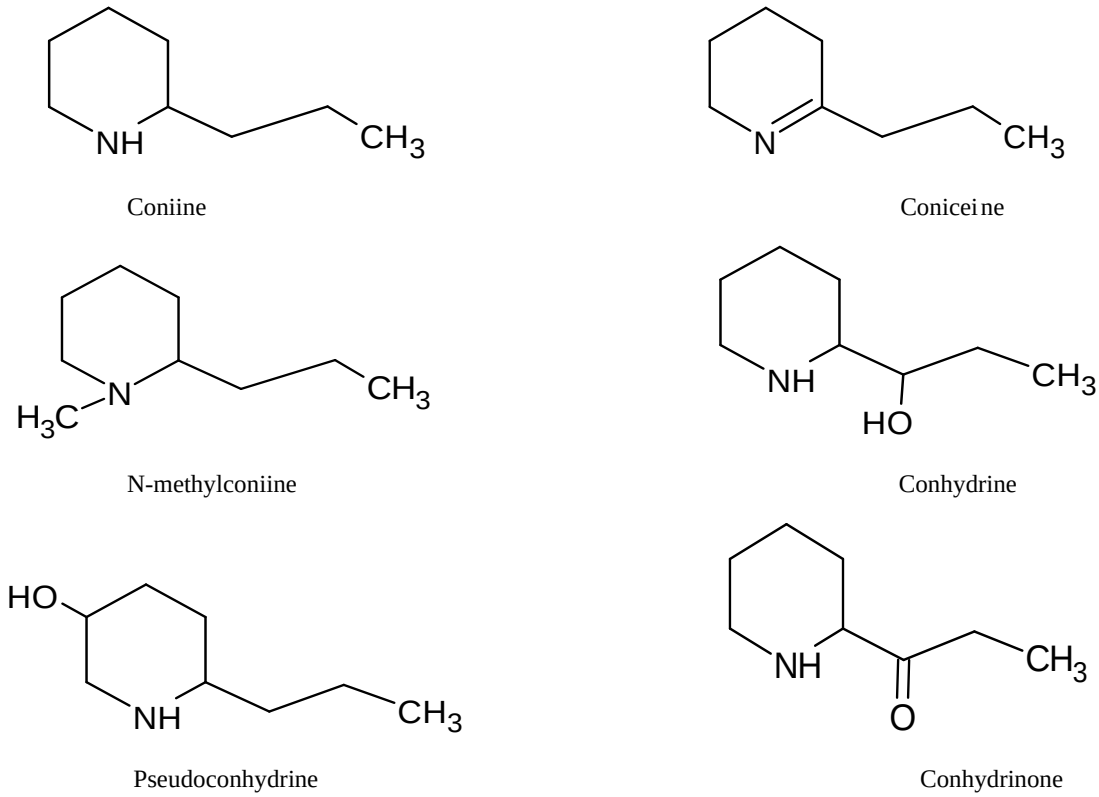

Figure 4. Some piperidine alkaloids present in *Conium maculatum* [73].

7.3. Anticancer Activity

In vitro studies have demonstrated the anticancer potential of *C. Maculatum* extracts against cancer cells. Conium, a piperidine alkaloid found in the plant, has been shown to interact with DNA and impede the proliferation process and cell cycle. Treatment with conium resulted in decreased viability and colony formation of HeLa cells, as well as an accumulation of reactive oxygen species (ROS) and depolarization of the mitochondrial membrane. Additionally, conium treatment led to morphological changes in HeLa cells, fragmentation, and modulation of proteins related to cell proliferation and apoptosis. The mechanism of apoptosis is believed to be related to the upregulation and downregulation of specific proteins. These findings suggest that *C. Maculatum* extract may have the potential as an anticancer agent[74].

Conium upregulated reactive oxygen species (ROS) activity by stopping cell division early in conium, demonstrating its growth inhibitory effect on cancer cells. Incidentally, proliferation is mainly promoted by the protein pAkt/Akt[75].

7.4. Toxicological Properties

Hemlock (*C. maculatum*) is a highly toxic plant due to piperidine alkaloids in all plant parts, including leaves, flowers, fruits, seeds, and roots[76]. Human poisoning has been reported following ingesting the plant's leaves, roots, or seeds. Symptoms of *C. maculatum* poisoning in humans include rapid loss of lower limb strength (muscle weakness), ataxia, staggering, and tremors. As the effects intensify, there is a loss of control of the upper limbs, total paralysis of legs and arms, loss of ability to chew and loss of sensation, fixed pupils, slow and weak pulse (later becoming fast), rapid breathing, abundant salivation, frequent urination, nausea, convulsions, and a drop in body temperature. Ultimately, death occurs due to paralysis of respiration and asphyxia, with the intellect remaining clear until death. Acute renal failure appears to be a symptom specific to human intoxication, compared to animal intoxication[76].

The signs of acute *C. Maculatum* intoxication are similar across various animal species. Cattle, sheep, and swine exhibit symptoms such as muscle weakness, incoordination, tremors, mydriasis, pressing on the metacarpophalangeal joints, excessive salivation, cyanotic membranes, and cold limbs. The onset of these symptoms is followed by an initial stimulation of the central nervous system, followed by depression, and rapid and shallow breathing, which subsequently transitions to slow and labored breathing, dilated pupils, frequent urination and defecation, coma, and ultimately death due to respiratory paralysis[77].

7.5. Traditional Use

The medicinal uses of *Cicuta maculatum*, commonly known as water hemlock, are rare today. However, it was traditionally used in low doses to treat neuralgia, sciatica, and rheumatism. The plant is primarily used as an abortifacient as vaginal tampons in the regions of Casablanca and Rabat in Morocco. It is also known for its toxic properties. In the Rabat region, fumigations made from the root of water hemlock were used to treat venomous stings and bites[78].

8. *Lawsonia inermis* (*L. inermis*)

8.1. Geographical Location

Lawsonia inermis, commonly known as henna or mehendi, is a small tree that is primarily cultivated for its leaves. However, the stem bark, roots, flowers, and seeds of the plant have also been utilized in traditional medicine, and it is commonly found in tropical

and subtropical regions. The plant has a long history of use in traditional herbal medicine, particularly in Ayurvedic medicine in India, as described in ancient texts. The plant is native to North Africa and South-West Asia[79]. It is worth noting that the plant is native to the regions of North Africa and South-West Asia[80].

8.2. Phytochemical composition

2-Hydroxy-1, 4-naphthoquinone (HNQ; Lawsone) is the primary natural pigment in henna leaves, comprising 1.0 to 1.4% of the leaf's composition. Other related compounds present in the leaves include 1,4 dihydroxynaphthalene, 1,4-naphthoquinone, 1,2-dihydroxyglucoyloxynaphthalene, and 2-hydroxy-1,4 diglucosyloxynaphthalene, in addition to flavonoids (such as luteolin, apigenin, and their glycosides), coumarins (such as esculetin, fraxetin, and scopoletin) and steroids (such as β sitosterol)[81]. Additionally, *Lawsonia inermis* leaves have been found to contain a variety of other compounds, including tannin, gallic acid, glucose, mannitol, fat, resin, and mucilage[82].

The plant's bark contains various compounds, including naphthoquinone, isoplumbagin, triterpenoids, hennadiol, and aliphatics (such as 3-methylnonacosan-1-ol). Steam distillation of the flowers has yielded an essential oil with a concentration of 0.02%, rich in ionones, with β-ionones predominating[74].

The essential oil primarily comprises aliphatic esters, with relatively few terpenoids present. The major components of the oil include ethyl hexadecanoate (24%), (E)-methyl cinnamate (11.4%), and methyl linoleate (4.1%). Other terpenoids present in significant quantities include isocaryophyllene (8.1%), (E)-β-ionone (5.8%), nerylacetone (4.4%), and α-terpineol (3.9%). The leaf oil compositionfound to differ significantly from that of the plant as a whole[82] and the flowers precisely[83].

The β-ionone compound was quantified at 48.6% and 2.5% concentrations in the yellow and red flower essential oils, respectively. However, it was found to be completely absent in the essential oil derived from the entire plant. Despite this, the violet odor compound (La β-ionone) was found to occur at a relatively low concentration (5.8%) in the leaf oil. Additionally, linalool, which constituted a significant portion of the yellow and red flower oils (19.8% and 12.7%), was detected only in limited amounts (0.7%)[82].

8.3. Anticancer Activity

The plant *Lawsonia inermis* has a long history of usage as a traditional medicine for cancer treatment. Additionally, it has been discovered to have potent anticancer

properties[84]. The compound lawsone found in *L.inermis* has been demonstrated to possess cytotoxic properties[85].

A study utilizing a crude dichloromethane extract of *L. inermis* leaves found it to exhibit significant cytotoxic activity against the human breast cancer cell line MCF-7 and the human liver cancer cell line HepG2[86]. An ethanolic extract of *L. inermis* also increased the life span of mice bearing Dalton's lymphoma as cited tumors[87].

Qian Lian *et al*. isolated new compounds of bicoumarin, biflavonoid, and biquinone, as well as twelve other known compounds from 4 to 15 (as shown in Figure 5), from the dichloromethane (DCM) extract of *L. inermis* flowers through a series of chromatographic techniques including silica gel, Sephadex LH-20, RP-18, and semipreparative HPLC.

The inhibitory effects of these compounds on the MCF-7, HeLa, HCT-116, and HT29 cancer cell lines were determined using the MTT (tetrazolium salt) assay. Compounds 3, 4, and 5 (as shown in Figure 5), which can be structurally classified as 1,4-naphthoquinones, exhibited significant inhibitory activity. In particular, compounds 3 and 5 showed more potent inhibitory activities than the chemotherapy drug 5-FU.

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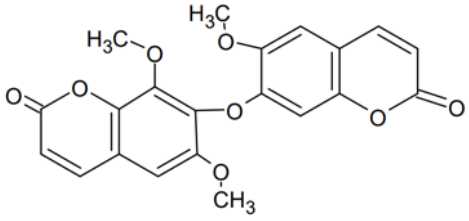

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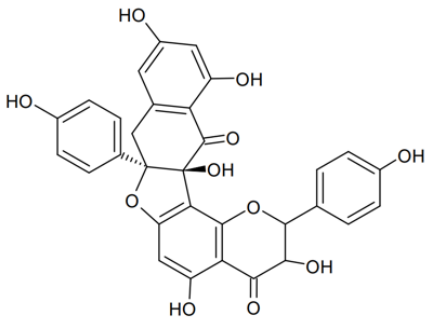

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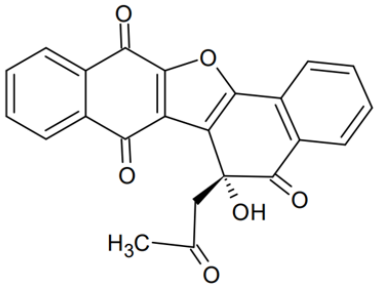

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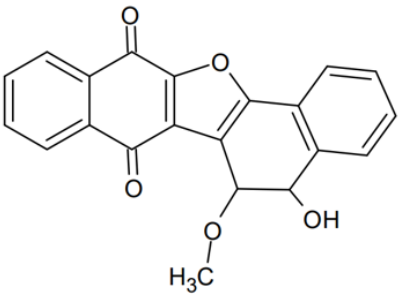

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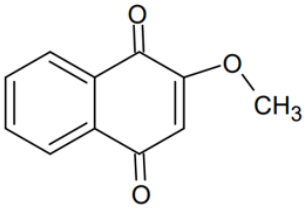

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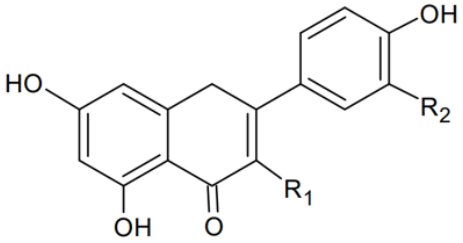
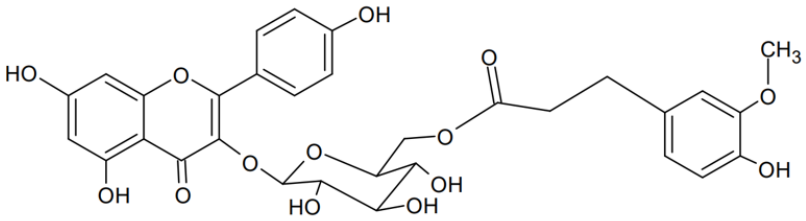


6 R_1=OH R_2=H

7 R_1=OH R_2=OH

8 R_1=OH R_2=OH



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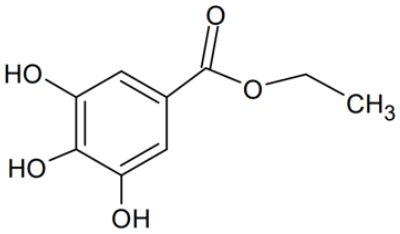

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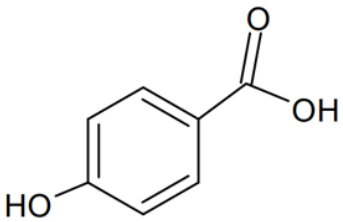

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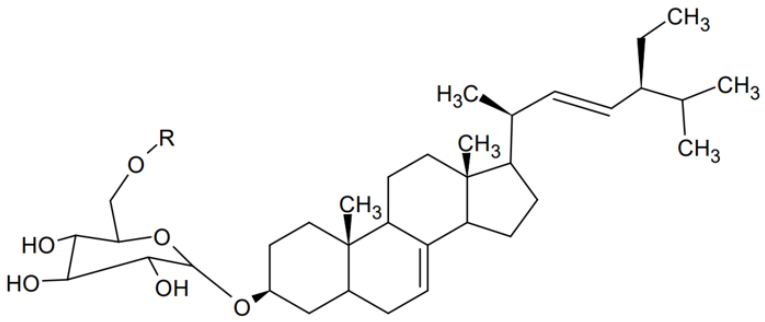
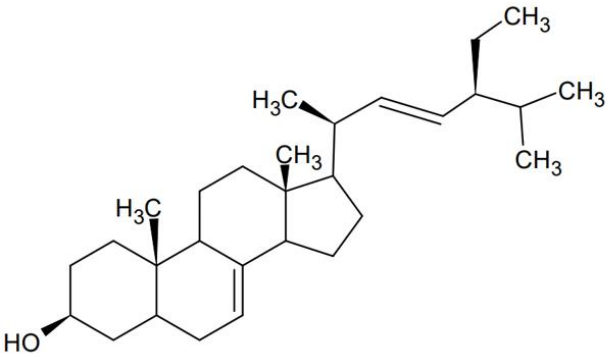


12 R= $(CH_2)_{15}CH_3$



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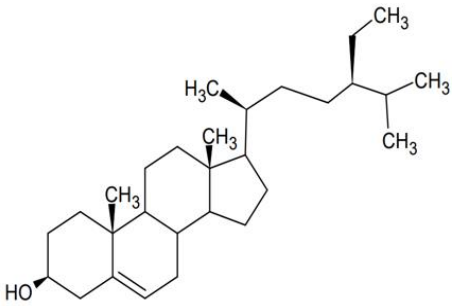


14

15

Figure 5. Structures of compounds 1–15.

8.4. Toxicological Properties

Henna is a substance with little or no toxicity, mainly when applied to the skin. Given its widespread cosmetic use worldwide over the centuries, and the relatively few allergic reactions reported in the literature, henna is generally considered to be a weak sensitizing agent. Studies have shown that an aqueous extract of *L. inermis* root is slightly toxic when administered orally, causing delayed toxicity symptoms such as paralysis, total body collapse, weakness, sluggishness, and loss of appetite without resulting in death. Lawsone, which is considered to be the active component of henna, has been identified as

responsible for its haemotoxicity[89].

When administered to rats, lawsone has been shown to cause decreased hematocrit, reduced hemoglobin level, and an increased spleen weight/liver weight ratio. Based on these observations, it is suggested that Lawsone is responsible for the observed physiological changes and has been shown to induce oxidative stress related to hemolytic anemia when administered to rats[90].

8.5. Traditional Use

Henna is used in traditional Moroccan medicine as a component in infusions to treat conditions such as kidney stones, diarrhea, and ulcers. Additionally, it is commonly used in poultices to treat skin conditions such as eczema, mycosis, boils, abscesses, and chapped skin. It is also considered to have astringent, antiseptic, and wound-healing properties and is used to treat umbilical wounds of newborns. Henna also treats sprains, dislocations, stretched ligaments, and fractures[91].

9. *Nerium oleander* (*N. oleander*)

9.1. Geographical Location

N. oleander, also known as Defla in the Maghreb and the Arab world, is a shrub commonly found in the Mediterranean region, particularly along waterways in Morocco. It is native or naturalized in a wide geographical area, including regions from Mauritania, Portugal eastward, through the Mediterranean region and the Sahara (occurring only sporadically), to the Arabian Peninsula, the east coast of the United States, South Asia, and as far south as Yunnan in China[92].

9.2. Phytochemical composition

The most abundant components found in the flower essential oil of *Nerium oleander* were neriine (22.56%), followed by digitoxigenin (11.25%), amorphane (8.11%), 1,8-cineole (6.58%), α-pinene (5.54%), Calarene (5.12%), Limonene (5.01%), β-Phellandrene (4.84%), Terpinene-4-ol (3.98%), Sabinene (3.22%), Isoledene (2.94%), 3-Carene (2.56%), Humulene (2.29%), β-Pinene (2.01%) and Cymen-8-ol (1.67%). The well-known effects of *N. oleander* are primarily attributed to two glycosides, neriine, and oleandrin alkaloid, which have a cardio-stimulant action[93]. Other glycosides such as gentiobiosyloleandrin, gentiobiosylnerigoside and gentiobiosylbeaumontoside extracted from the leaves, have also been found to have diuretic effects and to be effective in treating dermatitis and bruises[94].

Furthermore, the sap of *Nerium oleander* is known to be rich in minerals[95], and α-tocopherol. The plant also contains weakly active cardenolides (such as uzarigenin heterosides), inactive cardenolides (such as adynergenin heteroside and digitalose), triterpenoids, resin, tannins, glucose, kerosene, ursolic acid, and vitamin C. The seeds contain glucosides, including oleandrin, odorosides, and adigoside. The plant's bark also includes glucosides, including rosaginoside, nerioside and corteneroside, and the roots contain steroids[96].

9.3. Anticancer Activity

Nerium oleander is commonly used in traditional medicine as an anti-cancer agent. The observed anticancer activities of isolated cardenolides and crude extracts support their use in traditional medicine. The monoglycosidic cardenolides are among the most potent anticancer substances found in the plant. A cold water extract of *N. oleander* leaves has been tested on more than 380 cancer patients since 1988 with promising results[97,98]. The observed cytotoxic effects are believed to be caused by the inhibition of the Na+ / K+ -ATPase enzyme bound to the plasma membrane[99,100].

9.4. Toxicological Properties

All parts of *Nerium oleander* contain cardiotonic glycosides whose action on the heart is similar to that of Digitalis purpurea (foxglove). Poisoning can occur after ingesting even small amounts of plant material. However, the toxic dose varies depending on several factors, such as the concentration of glycosides in the plant, the amount ingested, the age, and the individual's health condition. Accidental exposures typically do not result in severe poisoning, as children are unlikely to consume large amounts due to the bitter taste of the leaves[101].

9.5. Traditional use

In Morocco, the roots of *Nerium oleander* are traditionally used in fumigations to treat headaches, common colds, and diseases of the uterus. The plant stems are also used in traditional medicine to create points of fire for treating rheumatism, and articular and joint pains[102].

10. *Nigella sativa* (*N. sativa*)

10.1. Geographical Location

Nigella sativa L. (commonly known as black cumin or "habbet el-baraka," meaning "seed of divine grace"), belongs to the family Ranunculaceae. It is native to the region of Asia Minor, including countries such as Syria, Turkey, Saudi Arabia, Pakistan, and India. The plant is cultivated in the Mediterranean region for its seeds, as well as for ornamental purposes. Additionally, *N. sativa* L. Is also widely cultivated in Morocco[103,104,105].

10.2. Phytochemical Composition

Houghton *et al*. demonstrated a diverse array of natural compounds in Nigella sativa, including lipids, terpene derivatives, flavonoids, alkaloids, and saponins. Additionally, *N. sativa* is an essential source of proteins and minerals[106].

N. sativa seeds have been found to contain 36-38% fixed oil, protein, alkaloids, saponin, and 0.4–2.5% essential oil[107]. The fixed oil primarily comprises unsaturated fatty acids, including arachidic and eicosadienoic acid[108].

The essential oil of *N. sativa* has been analyzed by Brits and Bucar using GC/MS. Several components have been identified, with the main ones being thymoquinone (27.8%–57.0%), ρ-cymene (7.1%–15.5%), carvacrol (5.8%–11.6%), t-anethole (0.25%–2.3%), 4-terpineol (2.0%–6.6%) and longifolia (1.0%–8.0%). Thymoquinone is reportedly readily dimerized form dithymoquinone [109,110]. Four alkaloids have been identified as constituents of *N. sativa* seeds, including nigellicin and nigellidine (Figure 6)[111,112].

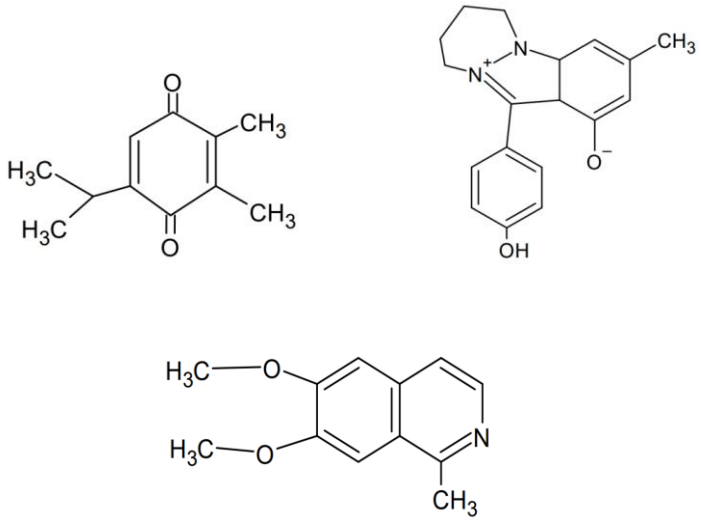


Figure 6. Chemical structures of some major constituents of *N. sativa* seeds.

10.3. Anticancer Activity

The anti-cancer properties of *Nigella sativa* have been primarily attributed to its ability to exert potent antiproliferative, pro-apoptotic, antioxidant, antimutagenic, and anti-metastatic effects. Many of these anti-cancer activities have been linked to the plant's principal active compound, thymoquinone (TQ). Studies have shown that TQ possesses antiproliferative, pro-apoptotic, antioxidant, antimutagenic, anti-angiogenic, and anti-metastatic effects against various cancer cell lines[113,114]. TQ is believed to mediate these anti-cancer effects by targeting multiple cellular pathways, including p53, NF-kB, PPARg, STAT3, MAPK, and PI3K/AKT signaling pathways[115,116].

In addition to thymoquinone (TQ), other phytoconstituents of *Nigella sativa* have also been shown to contribute to the plant's anti-cancer potential. For example, α-hederin, a pentacyclic triterpene saponin found in *N. sativa* seeds, has been demonstrated to possess practical anti-cancer effects in both in vitro and in vivo studies[117,118].

Other phytoconstituents of *N. sativa*, such as thymol, thymohydroquinone, dithymoquinone, nigellimine-N oxide, nigellicin, nigellidin, and carvacrol, have also been shown to possess anti-cancer and cytotoxic properties. However, further research is needed to fully understand the mechanisms of action that mediate the anti-cancer effects of these phytoconstituents, as the molecular processes behind these effects are not yet fully understood[119,120].

10.4. Toxicological Properties

Acute administration of high doses of *Nigella sativa* seed extract (2g/kg or higher) has been found to cause hypoactivity and respiratory difficulties in animals. These high doses have been found to decrease levels of the antioxidant glutathione (GSH) in the liver, kidney, and heart and cause harm to the liver and kidney, as indicated by significant increases in plasma metabolites and enzymes[121]. However, when thymoquinone, one of the active compounds found in *N. sativa*, was included in the drinking water of mice at concentrations of up to 0.03% for 90 days, no signs of toxicity were observed, except for a significant decrease in plasma glucose concentrations[122].

Toxicity studies in animals have revealed that nigella intake can alter blood parameters such as hemoglobin metabolism, white blood cell, and platelet levels. Additionally, total black cumin oil has been found to inhibit certain pro-coagulant prostaglandins, potentially increasing the risk of bleeding. It is also reported that black cumin may have abortifacient properties during the first ten days of pregnancy, but this

effect has not been observed beyond this period. However, it is essential to note that these studies were performed on animals, and more research is needed to determine the potential effects of *Nigella sativa* in humans[123].

10.5. Traditional Use

In Morocco, the powder made from freshly ground *Nigella sativa* seeds is commonly used for various medicinal purposes. These include inhalations for colds, flu, migraines, sinusitis, pulmonary conditions, and asthma. The powder is used as an ointment to treat various skin conditions, such as varicose veins, corns, vitiligo, scabs, hemiplegia, facial paralysis, and limb paralysis. The powder is also applied to the teeth for relief from dental pain. At low doses, *Nigella sativa* seed powder has traditionally been used as a galactagogue, warming agent, anti-nausea, strengthening agent, vermifuge, emmenagogue, antipyretic, and venom. However, it is essential to note that the medicinal properties of *Nigella sativa* have not been extensively studied, and more research is needed to confirm the effectiveness of these traditional uses[124].

11. *Marrubium Vulgare (M. Vulgare)*

11.1. Geographical Location

Marrubium vulgare L. (white horehound) is a perennial flowering plant native to North Africa, Europe, and Asia. It has been introduced to other regions, such as Japan, southern Africa, America, Australia, and New Zealand, and has been reported to be invasive in many of these territories. However, it is essential to note that invasive species can negatively impact native ecosystems and should be carefully monitored[125].

11.2. Phytochemical Composition

The yield of essential oil obtained from the aerial parts of *Marrubium vulgare L.* through hydrodistillation was found to be 0.34%. The main chemical compounds identified in the oil were γ-eudesmol (11%), germacrene (10%), D-citronellyformate (10%), β-citronellol (8%), geranyl tiglate (7.1%), and geranyl formate (6.02%). Other compounds present in smaller percentages include lendene (5.15%), cyclononasiloxane-octadecamethyl (4.3%), 1,8-cineole (3.75%), geraniol (3.70%), neryl acetate (3.41%), γ-cadinene (3.35%), and B-cubebene (3.30%)[126]. Diterpenoids were the top class of compounds present in the aerial parts of *M. vulgare*[127].

Flavonoids are an important class of compounds that are widely distributed in different parts of *Marrubium vulgare* L[128]. Trace amounts of alkaloids, ursolic acid (a pentacyclic triterpene) and steroids have also been reported in the aerial parts of *M.*

vulgare[128]. In 2010, a study reported the isolation of a few normal alkanes and four types of branched alkanes from the aerial parts of *M. vulgare*[129].

11.3. Anticancer Activity

A study by Mehmet Evren OKUR *et al*. found that the cytotoxic effects of the methanolic extract of *Marrubium vulgare* L. at a dose of 1mg/mL on U87, LN229, and T98G glioblastoma multiforme (GBM) cell lines resulted in the viability of 69.9% and 71% for U87 and LN229 cells, respectively[130]. In addition, another study found that the essential oil of *M. vulgare* tested in vitro (using the MTT assay) was cytotoxic against a cervical cancer cell line, HeLa. The essential oil of *M. vulgare* was found to inhibit the proliferation of HeLa cells[131].

Zied Zarai *et al*. found that the ethanolic extract of *Marrubium vulgare* L. showed cytotoxic effects by reducing the viability of melanoma (B16) and glioma (U251) cells in a dose-dependent manner[132]. Additionally, the essential oil of *M. vulgare* was tested at different concentrations (3.91–3000 μg/mL) and was found to reduce the viability of HeLa cells significantly. The study reported that 250 μg/mL of the essential oil could destroy 27% of HeLa cells, and concentrations above 500 μg/mL destroyed all HeLa cells. At lower doses, the cells tolerated the oil, and the IC_{50} (the concentration at which 50% of cells are killed) was found to be 0.258 μg/mL[133].

11.4. Toxicological Properties

Marrubium vulgare L. may contain toxic agents such as psoralen, 8-methoxypsoralen, and 5-methoxypsoralen that are responsible for adverse reactions. A study by K. El Morabite *et al*. found that using the plant for analgesic purposes could lead to dermal lesions similar to chemical burns, which could induce dermal-epidermal cleavage up to the formation of vesiculo-bubbles[134].

Health risks have also been associated with the handling or ingesting of plants containing psoralen and xanthotoxin. Studies in animals have shown that the administration of psoralen, bergapten (5-methoxypsoralen), and xanthotoxin (8-methoxypsoralen) in female rats may cause a reduction in ovarian follicular function and ovulation[135].

11.5. Traditional Use

In Morocco, the decoction of *Marrubium vulgare L*. is traditionally used as an

antidiabetic treatment, either alone or in combination with other plants such as fenugreek, white wormwood, white lupine, thyme, and rue. The juice of the fresh plant is also used for this purpose. Additionally, the decoction is used as an antityphoid, antidiarrheal, febrifuge, diuretic, emmenagogue, anti-icteric, expectorant, tonic, and stimulant for bedridden patients. The plant is also commonly used in cataplasms applied to the forehead for fever and on abscesses and furuncles to promote healing[134].

12. *Myristica fragrans (M. fragrans)*

12.1. Geographical Location

Myristica fragrans Houtt. is an evergreen tree native to the Moluccas (or Spice Islands) in Indonesia. It is widely cultivated in tropical regions, including Guangdong and Yunnan in China, Taiwan, Indonesia, Malaysia, Grenada in the Caribbean, Kerala in India, Sri Lanka, and South America[136].

12.2. Phytochemical Composition

The fresh pericarp, or rind, of the ripe fruit of *Myristica fragrans* Houtt. contains an acidic, astringent juice with a distinctive flavor. Analysis of the composition of the fruit rind has revealed the presence of protein, fat, minerals, phosphorus, iron, and carotene[136]. Additionally, the rind contains up to 14% pectin and 27% fiber[137].

Phytochemical analysis of *M. fragrans* has revealed the presence of various compounds, including essential oil, which makes up about 10% of the seed[138]. A neolignan compound called Dihydro-diisoeugenol has been isolated from the hexane and chloroform extract of the arils[139]. Furthermore, five phenylpropanoids have been reported in the seed core of the plant, and dihydroguaiaretic acid has been isolated from the nutmeg mass[139,140].

The essential oil of *Myristica fragrans* Houtt. from India was subjected to GC-MS analysis, which revealed the presence of 49 compounds. The major constituents identified were sabinene (20.2%), terpinen-4-ol (12.1%), safrole (6.1–10.3%), alpha-pinene (9.7%), phellandrene (6.6%), and gamma-terpinene (5.9%)[141]. A study by M. Pal *et al*. reported that terpinen-4-ol (15.0%), sabinene (13.1%), and gamma-terpinene (11.2%) were found to be the major constituents of the essential oil of *M. fragrans* from Brazil[142].

Additionally, the main volatile components of *M. fragrans* collected from the Andaman and Nicobar Islands were sabinene (41.7%), alpha-pinene (9.4%), and alpha-pinene (7.3%), terpinene-4-ol (5.8%), limonene (3.7%), and myristicin (2.7%). It is

important to note that the composition of the essential oil of *Myristica fragrans* may vary depending on factors such as geographic location, soil, climate conditions, and plant variety[143].

12.3. Anticancer Activity

Studies have shown that nutmeg extracts from *Myristica fragrans* can suppress the growth of human lymphoid leukemia cells, Molt 4 B[144]. Dihydroguaiaretic acid, a compound found in *M. fragrans*, has been shown to inhibit the growth of leukemia, colon cancer, and lung cancer cells in vitro[145].

Myristicin, a component of the essential oil of *M. fragrans*, has been identified as a potential cancer chemopreventive agent[146]. Additionally, the mass of *M. fragrans* has been found to protect against bone marrow genotoxicity in male Swiss albino mice[147]. The animal model studies indicated the essential oil of *M. fragrans* may have chemopreventive effects against dimethylbenz(a)anthracene (DMBA) papillomagenesis in mouse skin. They can modulate the formation of DNA adducts by aflatoxin in vitro[148,149].

12.4. Toxicological Properties

Toxicity studies have shown that consuming *M. fragrans* can lead to adverse effects such as weak pulse, hypothermia, delirium, dizziness, and nausea[150]. Moteki H and colleagues have reported teratogenic effects in rat fetuses exposed to nutmeg. Additionally, studies have found the formation of DNA adducts in the livers of adult and fetal mice treated with nutmeg, mace, or myristicin extracts, the primary constituent of the spice nutmeg. Safrole, a minor component of nutmeg, has also been found to produce DNA adducts in the liver of mice[151].

12.5. Traditional Use

Myristica fragrans, or nutmeg, is a perennial evergreen tree native to Indonesia's Moluccas (or Spice Islands). It is widely cultivated in tropical regions worldwide for its seeds, which contain essential oil and other phytochemicals.

Traditional uses of *M. fragrans* include treatment for digestion and sexual dysfunction, as well as for general weakness and respiratory conditions. In traditional medicine, the powdered seed is often mixed with honey and consumed orally to treat gynecological disorders[152].

13. *Peganum Harmala (P. Harmala)*

13.1. Geographical Location

P. Harmala L. is a perennial plant belonging to the family Zygophyllaceae, native to the Middle East, North Africa, and Southern Europe. It is commonly found in steppe regions, highlands, and the Sahara. The plant displays linear, alternate, and sessile leaves and white flowers with five oval petals and numerous yellow stamens. The plant is called "l-harmel" in the Arab world[153].

13.2. Phytochemical Composition

The phytochemistry of *P. Harmala* includes the presence of alkaloids, flavonoids, and anthraquinones[143]. The major beta-carboline alkaloids in *P. Harmala* extracts include harmalin, harmine, harmalol, harmol, and tetrahydroharmine. The total alkaloid content of *P. Harmala* ranges from 2-5%, with the highest concentrations found in the seeds and roots and lower levels in stems and leaves. Notably, flowers do not contain significant levels of alkaloids. Studies have shown that harmine and harmaline are present in dry seeds at 4.3% and 5.6% (w/w) respectively, harmalol at 0.6% and tetrahydroharmine at 0.1% (w/w). The roots contain harmine and harmol with 2.0% and 1.4% (w/w), respectively[154].

Phytochemical analysis of *P. Harmala* has revealed the presence of alkaloids, flavonoids, and anthraquinones. The major beta-carboline alkaloids in *P. Harmala* extracts include harmalin, harmine, harmalol, harmol, and tetrahydro harmine. The total alkaloid content of *P. Harmala* ranges from 2–5%, with the highest concentrations found in seeds and roots. Additionally, Peganin, isopreganine, dipeganin, and deoxypeganin have been identified in P. Harmala. The plant also contains quinazoline alkaloids such as vasicine and vasicinone, and a new β-carboline alkaloid, harmalidine, and pegamine, were also isolated from seeds and aerial parts of *P. Harmala*.

Phytochemical analysis of *P. Harmala* has revealed the presence of alkaloids, flavonoids, and anthraquinones. The major beta-carboline alkaloids in *P. Harmala* extracts include harmalin, harmine, harmalol, harmol, and tetrahydro harmine. The total alkaloid content ranges from 2-5%, with the highest concentrations in seeds and roots[155,156].

Additionally, Peganin, isopreganine, dipeganin, and deoxypeganin have been identified in P. Harmala. The plant also contains quinazoline alkaloids such as vasicine and vasicinone, and a new β-carboline alkaloid, harmalidine and pegamine, were also isolated from seeds and aerial parts of *P. Harmala*[155,157,158]. The alkaloids vasicine and vasicinone,

both members of the quinazoline class, were initially discovered in the flowers and stems of P. harmala. A new β-carboline alkaloid derivative, characterized as l-thioformyl-8-β-D-glucopyranoside-bis 2,3-dihydroisopyridinopyrrol, was isolated from the aerial parts of P. harmala. Analysis of the aerial parts of *P. harmala* revealed the presence of four flavonoids, including 7-O-rhamnoside acetin, 7-O-6"-O-glucosyl-2"-O-(3"'-acetylrhamnosyl) glucoside, 7-0-(2"'-0-rhamnosyl-2"-O-glucosylglucoside) and 2"'-O-rhamnosyl-2"-O-glucosylcytisosideglycoflavone[159].

Additionally, two anthraquinones were isolated from *P. harmala* seeds and identified as 3,6-dihydroxy-8-methoxy-2-methyl anthraquinone (peganone1) and 8-hydroxy-7-methoxy-2-methyl anthraquinone (peganone2)[160].

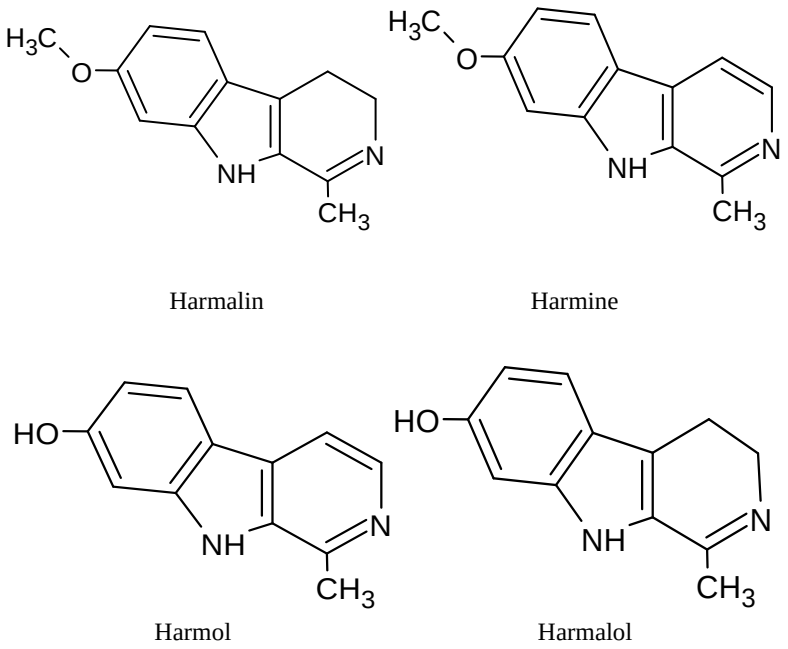


Figure 7. Some alkaloid content of *P. Harmala*.

13.3. Anticancer Activity

P. harmala has been extensively reported in traditional medicine as a treatment for various diseases, including cancer[161]. Previous studies have demonstrated the cytotoxic effects of crude seed extracts of *P. harmala*, including aqueous, hydroalcoholic, and methanolic extracts, suggesting a significant cytotoxic potential[162,163]. The high alkaloid content of *P. harmala* extracts has prompted research into their potential cytotoxicity[164].

The activities of the aerial parts, fruit, and roots of *P. harmala* against several cancer cell lines, namely A549, U373, Hs683, MCF7, B16F10, and SKMEL-28, have not been studied previously. The results from a recent study demonstrated that extracts of total

alkaloids from fruits, seeds, roots, and aerial parts decreased the viability of all analyzed cancer cell lines in a dose-dependent manner. The total alkaloid extract (TAR) significantly reduced cancer cell viability. These results suggest alkaloids are a primary class of compounds in different parts of *P. harmala* and are likely responsible for the observed cytotoxic effects. The differences in activity between the other parts of the plant are likely due to variations in alkaloid composition, and a synergistic effect of different alkaloids cannot be excluded[159]. The alkaloids extracted from *P. harmala* samples inhibit the viability of the breast cancer cell line (MCF7) at a concentration (IC_{50}) lower than the IC_{50} value reported for total alkaloid extracts of seeds obtained from Iranian *P. harmala* (cell line MCF7; IC_{50} = 25g/mL)[165].

The components of *P. harmala L.*, the beta-carboline alkaloids harmine and harmaline, have opposing effects on the viability of tumor cell lines. Harmine has been observed to have no impact on the cell viability of several cell lines such as HeLa, C33A, SW480, and CCD-18Lu. In contrast, harmaline has been found to significantly reduce the cell viability of control and malignant cell lines in a dose-dependent manner[166].

13.4. Toxicological Properties

All parts of the *P. harmala* plant are toxic. Previous studies have demonstrated adverse side effects such as heightened respiration, heart rate, and clonic muscle spasms in cattle following intravenous injection of harmine and harmaline (9 mg/kg)[167]. *P. harmala* poisoning has been observed in all domestic animals, with young camels particularly susceptible during dry seasons[168].

Animals that have ingested sublethal doses of *P. harmala* have exhibited signs of digestive and neurological diseases[160]. A study by Shapira *et al*. investigated the effects of a methanolic extract of *P. harmala* on the reproduction of female rats. The results showed that administering the extract at a dose of 2.5 g/kg/day for 30 days in meal suspension or suspension significantly extended the diestrus phase by ten days, while the estrous stage duration remained constant. Furthermore, the methanolic extract reduced the number of live pups and increased the number of resorptions[169].

13.5. Traditional Use

P. harmala has been traditionally used as an emmenagogue and abortifacient[170]. The plant's seeds (chebba wa l-harmel) are also believed to protect against the evil eye and evil spirits in certain cultures. In Marrakech, Rabat, Salé, Casablanca, and Tissint, it is also

used to treat conditions such as icterus, colds, hemorrhoids, intestinal pain, heart disease, female sterility, and uterine diseases. The plant seeds (harmel) are commonly used to treat infant toxicosis and childhood diarrhea[171].

14. *Taxus baccata (T. baccata)*

14.1. Geographical Location

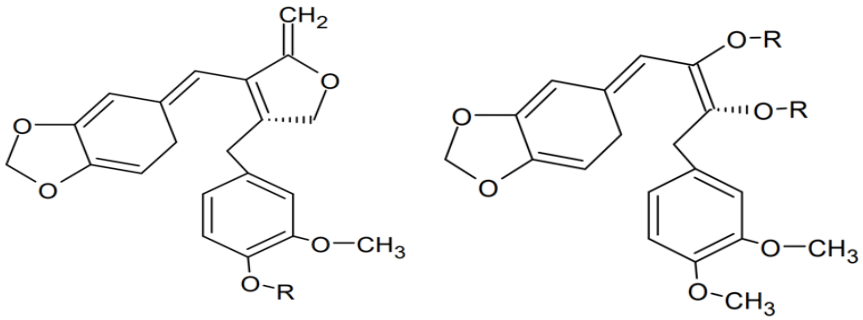
The geographical range of *Taxus baccata*, commonly known as the yew, covers central and southern Europe[172], Anatolia, the Caucasus, and the Elburz Mountains in Asia[173], and north-western Africa[174]. Madeira and the Azores[175]. In the Mediterranean region[176]. As for most other Euro-Saharan species, *T. baccata* is found primarily in the mountainous area[177].

In Morocco, *T. baccata* represents the Euro-Siberian geographical element of the flora[178]. The presence of this species in Morocco was first recognized by Jahandiez and Maire (1931) and Emberger (1938)[177]. It has been reported to occur between "Beni Jaled and Beni Syel"[179], more specifically in the Rif, the central part of the Middle Atlas and the High Atlas[180].

14.2. Phytochemical Composition

The composition of the essential oils extracted from *Taxus baccata*, commonly known as yew, revealed that aliphatic alcohols, terpenes, aliphatic hydrocarbons, and aliphatic aldehydes were the predominant compounds, contributing, on average, to 86.92% of the total oil composition. The terpene fraction was dominated by monoterpenes (14.41%), while sesquiterpenes represented only 2.31% of the essential oil. The most abundant constituents were two aliphatic alcohols, oct-1-en-3-ol and (3Z)-hex-3-en-1-ol, and an oxygenated monoterpene, myrtenol, with a total average content of 46.32%[181]. The twigs of *T. baccata* were also found to contain a mixture of phenols, taxoids, sterols, and fatty compounds in the dichloromethane-methanol extract (1:1). Phenolic compounds were the major constituents of the extract. A new lignan, 4'-Odemethylsuchilactone, was isolated as a yellow oil[182]. Additionally, three other lignans, suchilactone, diol 3, and (-)-secaisolariciresinol, were isolated. Suchilactone[~-(trans-3,4-methylenedioxybenzylidenefl-R-(3,4-dimethoxybenzyl)- ~ -butyrolactone] was isolated for the first time from a Taxaceae species[183].This compound was previously reported from two other species, Polygalachinensis and Haplophyllumpopovii, and as a pyrolytic product of Lignan'shelianthoidin[184,185].

Lignandiol 3, a compound not previously isolated from a natural source, was present in the twigs of *T. baccata*. It was prepared from suchilactone[186]. Upon acetylation with acetic anhydride and pyridine, it yielded a diacetate. The physical and spectral properties of the diacetate were found to be similar to prasanthalin, a compound previously isolated from Jatropha gossypiifolia. In addition, the twigs of *T. baccata* were found to contain the biflavonoid constituents sciadopytisin, ginkgetin, and kayaflavone (Figure 8)[73].



R 1 H
2 CH_3

R 3 H
4 Ac

Figure 8. Some biflavonoid constituents of twigs.

The taxoids present in the twigs of *Taxus baccata*, commonly known as yew, primarily consisted of rearranged 11(15-1) abieto-taxane skeletons, as indicated by their spectral data. Two pure compounds, brevifoliol and 13-decinnamoyl-taxchinin B[74], possessing this rearranged skeleton, were isolated, along with a small taxoid, 10-deacetylbaccatin III, that had the taxane structure. The diterpenoid constituents of the twigs were also found to primarily consist of the abieto-taxane backbone 11(15-1), and taxoids of this type of rearranged structure showed tubulin-binding activity, but not cytotoxicity, in vitro[187].

14.3. Anticancer Activity

The genus Taxus has attracted significant attention due to its content of diterpenic alkaloids, particularly taxol (also known as paclitaxel and registered under the tradename Taxol®BMS[Bristol-MyersSquibb]). The anticancer properties of taxol were first discovered in extracts of *T. baccata* and *T. brevifolia* in 1971. The anticancer activity of taxol is primarily attributed to its side chain, a C2 benzoyl group, and an oxetane ring. The C3 amide-acyl group is also believed to contribute to its activity in the C13 chain. Its cytotoxic action is further enhanced by a hydroxyl group at C2[188].

Taxol, a diterpenic alkaloid found in the genus Taxus, binds to the surface of

microtubules, specifically the tubulin heterodimer subunit, and promotes the polymerization of these structures even in the absence of GTP (guanosine triphosphate)[189,190]. The interaction of taxol with the tubulin of microtubules leads to the promotion of polymerization and thus produces cytotoxicity and stabilization of microtubules. Taxol has been used primarily to treat metastatic ovarian carcinoma, metastatic breast cancer, and non-small cell lung cancer, as the number of cancers treated with taxol is increasing[191].

14.4. Toxicological Properties

A toxicity study of *T. baccata* leaf fractions and purified stem fractions in albino mice weighing 20–30g showed elevated levels of alkaline phosphatase and transaminase in mice treated with TXA-1 (methanolic extract of the leaf) and TXB- 1 (methanolic extract of the stem). These results indicate liver toxicity as an increase in transaminase (glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT)) and alkaline phosphatase (AP) is a common finding in liver disorders[192].

A marked elevation of serum glutamate oxaloacetate transaminase (SGOT) is commonly observed in cases of myocardial infarction and elevated serum glutamate pyruvate transaminase (SGPT) in cases of hepatocellular necrosis. This finding could likely be associated with the presence of taxanes and diterpene amides in the fractions used. It can be concluded that the crude drug, *T. baccata*, mainly the stem, is highly toxic, despite containing some therapeutic compounds. Therefore, the taxanes in different parts of *T. baccata* may represent a new potential tool for toxicological and pharmacological research[193].

14.5. Traditional Use

T. baccata, commonly known as yew, has been traditionally used as a medicine for treating rheumatism[194] and diabetes treatment[195]. In the Middle Atlas region of Morocco, a decoction made from the leaves is used as an abortifacient[196].

15. Conclusion

The current review focuses on the potential therapeutic value of several toxic plants that have demonstrated anticancer activities and are traditionally used in Moroccan medicine. Despite their toxicity, these 13 plants were found to have a variety of pharmacological and biological activities due to their diverse phytochemical compositions. Additionally, the study highlights the traditional uses of these toxic plants to treat various diseases in Morocco, which

warrants further investigation in preclinical and clinical trials to explore their potential therapeutic effects.

Moroccan cuisine often incorporates gruels, herbal drinks, and spicy drinks, which have been found to have numerous health benefits, including chemo-preventive properties and natural inhibitors of certain infections. When used appropriately and in conjunction with a healthy lifestyle, these traditional remedies may help reduce cancer incidence and provide therapeutic benefits for various human pathologies.

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