Unveiling the Phytochemical and Therapeutic Landscape of *Euphorbia Resinifera*: Prospects for Drug Discovery

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Abstract
Euphorbia resinifera, a member of the Euphorbiaceae family, is notable for its significant medicinal properties. Originally endemic to Morocco, this species has become cosmopolitan, spreading widely across tropical regions worldwide. This review focuses on the phytochemical properties of Euphorbia resinifera, providing a comprehensive overview of its diverse phytochemicals and their potential therapeutic applications. The review also highlights the potential for further exploration of phytochemicals in less-studied parts of the plant, such as the flowers. Our primary sources were peer-reviewed research articlesand reports from scientific databases including Scopus, PubMed, Web of Science, and SpringerLink identifying numerous novel compounds, particularly from the latex of Euphorbia resinifera. Various studies have investigated latex, while fewer studies have examined the whole plant, stem, leaves, flowers, and honey. This review underscores the need for detailed studies on the unexplored parts of Euphorbia resinifera and suggests that the identified phytochemicals, traditionally used in ethnomedicine, could be further investigated for drug development. Such research could lead to the discovery of new treatments for diseases that pose significant challenges to human health.

Keywords: Euphorbia Resinifera, Phytochemicals, Bioassays, Ethnomedicinal, Diseases, Treatment

Introduction

The Euphorbiaceae family is one of the largest plant families containing 7,500 species (Xu: Diterpenoids from the genus *Euphorbia*), including Euphorbia resinifera. Euphorbia is the most significant genus within the Euphorbiaceae family, comprising more than 2,000 species globally and more than 80 species in China (Chen et al.; Xu: Diterpenoids from the genus *Euphorbia*). One of the most significant medicinal plants in this genus is E. resinifera (Lawant and Winthagen). The Middle Atlas Mountain area is home to this

Moroccan native plant. This perennial plant has virtually square, four-sided stems that are adorned with tiny brown spines. It may reach a maximum length of 60 cm and resembles a cactus. When this plant is hurt, it releases latex with a milky colour. It has long been used in folk medicine to treat many variety of conditions including diabetes, injuries, inflammation skin diseases, and various malignancies (Bruyns et al.).

Pharmacological investigations carried out in vitro and in vivo have demonstrated that chemicals and extracts from E. resinifera latex exhibit a broad spectrum of biological properties. These include anticancer, neuroprotective, anti-inflammatory, immunomodulatory, and anti-leishmanial qualities.

Cancer is a serious global health concern, responsible for numerous deaths worldwide (Stratton et al.). Similarly, there are many other dreadful diseases prevailing which are difficult in curing. While advancements in treatment have been made for various diseases, one major drawback of current therapies is the severe side effects associated with chemically synthesized drugs (Lichota and Gwozdzinski). According to Nguyen et al., patients have significant adverse effects as nausea, alopecia, suppression of the bone marrow, and cellular mutations. Scientists and medical professionals are growing increasingly interested in medicinal plants and their byproducts since they may be used for both prevention and treatment of serious illnesses (Greenwell and Rahman). Because of their structural stability, plants and their byproducts usually exhibit high effectiveness with relatively little toxicity, various chemical structures, and secondary metabolites including flavonoids, alkaloids, and terpenoids (Nelson et al.; Haider et al.).

Euphorbium

According to Meng et al., Euphorbia resinifera Berg's air-dried latex is known as Euphorbium. This plant has been found to contain certain structurally intriguing diterpenes (Xu et al.: Chemical constituents from *Daphne giraldii*; Hernanz et al.). Wang et al. discovered new triterpenoids within the latex of Euphorbia resinifera. They extracted 9 unique chemicals, 6 euphane triterpenes (Euphrol A–D, H and I) and three tirucallane triterpenes (Euphrol E–G comprising four nor triterpenes) from the methanol extraction of Euphorbium, in addition to seven recognised compounds. Based on in-depth examinations of their UV, HR-ESI-MS, IR, 1D, and 2D NMR techniques, their structures were determined. There was a suggested biogenetic connection made to these substances. All of these Separates were tested for cytotoxicity in the cancer cell lines MCF-7, U937, &C6. A few of the chemicals showed mild cytotoxic effects.

Five novel triterpenoids, known as euphatexols C–G, were identified by (Li et al.: Euphatexols C - G, five new triterpenoids from the latex of *Euphorbia resinifera*) after they were separated from Euphorbia resinifera latex. Comprehensive spectroscopic investigation, including HRMS, IR, 1 D, and 2 D NMR data, was used to identify their chemical structures. Boutoub et al. evaluated the antioxidant activity and potential for enzyme inhibition of Euphorbia resinifera, Euphorbia officinarum, and their water-soluble extracts and honey. Regardless of the plant species, larger total phenols, improved antioxidant activities, and inhibitory effects on acetylcholinesterase, lipoxygenase, and tyrosinase were linked to the ratio of plant mass to the volume of solvent (1:100) and extraction duration (1–2 h). The aqueous extracts in vitro activity were consistently higher compared to that of the matching honey samples. In addition, euphorbium is utilised in the treatment of tuberculosis, dental cavities, nerves, and chronic pain (Parisi et al.). Numerous chemical classes have been identified in E. resinifera formulations through phytochemical research. The predominant class of phytocompounds in the latex extracts is represented by terpenoids.

Euphorbia Resinifera as a Traditional Medicine

E. resinifera is cited in many used traditionally against a variety of illnesses and ethnobotanical studies, particularly cancer. Additionally, it is used to treat hypoglycemia (Bouiamrine et al.) and diabetes (Belhaj et al.: Ethnobotanical and toxicology study of medicinal plants; Errajraji et al.). Additionally, this species is used as a hair care and for hair tonic (El Alami et al.; Merzouki et al.), both as an anti-inflammatory and a laxative, and to heal wounds (Kemboi et al.), as well as to heal poisonous bites (Belhaj et al.: Ethnopharmacological and

Ethnobotanical study of Medicinal plants; Bourhia et al.; Bouiamrine et al.). It is further employed in the treatment of intoxication, headache, weakness, gastrointestinal disorders, metabolic disorders, respiratory illnesses (such as the flu, allergies, asthma, etc.), circulatory disorders, and problems of the reproductive system.

The pharmacological activity of extracts from E. resinifera has been documented by numerous researchers. These include antioxidants (Benmehdi et al.; Boutoub et al.; Hanane et al.), antitumoral (Talbaoui et al.), antibacterial (Benmehdi et al.), antifungal (Benjamaa et al.), neuroprotective (Ezzanad et al.), against irritation and skin damage (Furst; Zayed et al.), and antileishmanial effects (Benjamaa et al.).

Moreover, additional research examined the enzymatic activity of tyrosinase, lipoxygenase, acetylcholinesterase, and xanthine oxidase (Hanane et al.), its liver effects, lysosome biosynthesis (Farah et al.), and clinical trials (Goldblum and Curtis; Kuehn; Mancera and Wadia; Renukadevi and Sultana; Zissu). To the best of our knowledge, however, there hasn't been much research done on the in vivo toxicity effects of E. resinifera extracts (Issiki et al.).

It is reportedly a well-known prescription in Morocco to use E. resinifera to cure many forms of cancer. Many Moroccan communities utilise this plant as a cancer therapy. El Alami et al. conducted ethnomedical research that examined the usage of this species as a cancer treatment by the inhabitants of North Atlas of Azilal, Morocco. Many people have utilised the whole plant as an anticancer, either fresh or dried (Bouiamrine et al.). According to Samouh et al., the resin can be used naturally to treat malignancies of the otorhinolaryngology (ORL), colon, breast, lung, and leukaemia. Additionally, they highlighted how patients at the oncology department of the University Teaching Hospital Ibn Rochd in Casablanca (Morocco) employ E. resinifera to combat cancer.

Remedies for cancer have been used in the Casablanca region of Morocco using infusions of resin, roots, stems, leaves, and bark. The inhabitants of Azilal and Beni Mellal in the High Atlas Mountains have been using the stems, which are free of latex and bark, orally to treat female genital cancer and breast cancer (El Alami et al.). Ground aerial components coupled with honey have been used orally to treat a range of cancer types (El Alami et al.; Kabbaj et al.). The same population has treated skin cancer externally with a drop of latex (El Alami et al.). Additionally, honey combined with ground aerial components is utilised to cure tumours by the population of Rabat (El Alami et al.).

Furthermore, to its antitumoural qualities, a handful of studies have shown that E. resinifera stems, leaves, blossoms, latex and fruits can be used to treat diabetes. People in the Central High Atlas Mountains of Morocco, the Middle Atlas Mountain chains, the centre of the Atlas chain of Azilal North, Khenifra, Ouarzazate, Tinghir South, Ifrane, Marrakech and Beni Mellal used various parts of the E. resinifera to treat diabetes (Belhaj et al.: Ethnobotanical and toxicology study of medicinal plants; Bouiamrine et al.; Belhaj et al.: Ethnopharmacological and Ethnobotanical study; Errajraji et al.; Fouad and Lahcen).

In the past, E. resinifera has also been utilised cosmetically. This species (fresh and dry entire plant) has been used as a laxative and cosmetic by the people living within the Mid Atlas, Ifrane, and Khenifra ranges of mountains (Bouiamrine et al.). E. resinifera is used as a hair tonic and conditioner by the people of Ksar Lakbir, in northern Morocco (Merzouki et al.). The therapeutic and cosmetic properties of E. resinifera on hair were validated by another ethnobotanical study conducted in the northern Atlas of Azilal (El Alami et al.).

Additionally, E. resinifera has reportedly been used to cure toothaches, inflammation, poisonous bites, and scorpion stings. It can be utilised for healing teeth in the Northern Azilal, which is situated in the Atlas Mountains' middle, according to research by El Alami et al. El Alami et al. performed study on the communities of Beni Mellal and Azilal people living in the Atlas Mountains, which corroborated this four years later. In this study, a single droplet of E. resinifera latex was utilised as a conventional toothache remedy. Further ethnobotanical studies on this plant have demonstrated that E. resinifera is used as an anti-inflammatory in traditional medicine.

The whole plant, both fresh and dried, is commonly acknowledged to have anti-inflammatory properties in the middle part of the Atlas Mountain ranges, Ifrane and Khenifra, (Bouiamrine et al.). The people who live in Azilal, in the heart of the Beni Mellal, and Atlas Mountains in the northwest of the Central High Atlas, have been using warm water combined with honey and latex to treat skin irritation (El Alami et al.; Alami et al.: Medicinal plants used for the prevention purposes). Certain components of E. resinifera have been employed as anti-poisoning agents in inclusion to their anti-inflammatory properties. The people who live in Morocco's Central and Upper Atlas region employ the fruits, stems, and blossoms of E. resinifera as a protection against poisonous bites (Belhaj et al.: Ethnopharmacological and Ethnobotanical study of Medicinal plants).

Dried areal parts powder has been used for treating goitre when combined with honey. Female vaginal cysts have been treated with milk juice, stem (without latex or bark), and a tiny drop of latex for warts. Digestive issues are treated using a mixture of seed powder and honey (El Alami et al.). The people living in Beni Mellal and Azilal in the Atlas Mountains have experienced further therapeutic benefits. According to El Alami et al., the population under investigation used E. resinifera combined with the honey to treat a variety of conditions, including headaches, weakness, yellowing, angina, rheumatism, cysts, respiratory disorders, problems with circulation, disorders of metabolism, digestive diseases, reproductive system and diseases of the body.

These researchers have established that several communities throughout multiple Moroccan areas employ E. resinifera in conventional medicine to address a variety of ailment, most notably cancer. Even though E. resinifera is used to treat the primary illnesses mentioned in all of these ethnobotanical research investigations, pharmacological activities, bioactive components, and toxicological studies must be thoroughly examined to fully understand this traditional medicine.

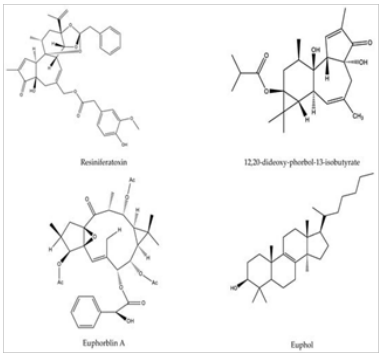
Beyond its native region, the plant's bioactive compounds, such as resinifera toxin, have gained global attention for their potential in management of pain and other medical applications. Additionally, phytochemical analyses of Euphorbia resinifera have identified terpenoids and flavonoids, which are responsible for its pharmacological properties, suggesting broader applications in cancer therapy and microbial inhibition (Govaerts et al.). Despite the focus on Moroccan studies, increasing research in other regions highlights its global significance, including its role in comparative studies of Euphorbia species in Europe and North America (Riina et al.).

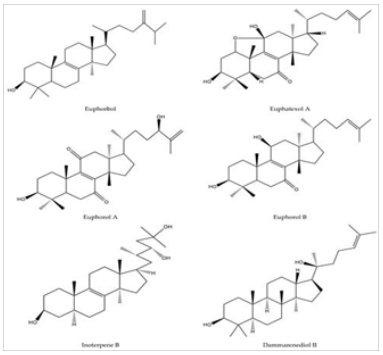
Phytochemistry

Numerous investigations have demonstrated that E. resinifera extracts, particularly latex extract, contain a wide range of chemical compositions (Boutoub et al.; Ezzanad et al.; Fattorusso et al.; Girin et al.; Mallon et al.; Mazoir et al.; Nordal and Benson; Ourhzif et al.; Qi et al.).

Terpenoids

Numerous terpenoids were identified as a result of earlier research examining the chemical constituents of E. resinifera extract (Figure 1) (Hmidouche et al.). This plant's latex contained the bulk of the detected terpenoids (Wang et al.).





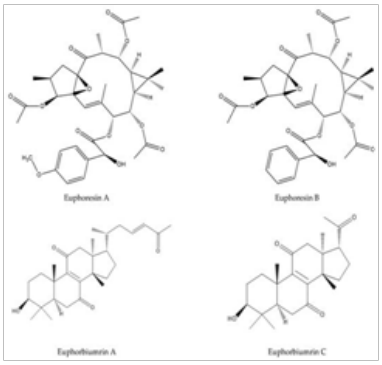


Figure 1 Chemical structure of terpenoids identified in E. resinifera latex (Oumaima)

The initial study, carried out in 1969 by Nordal and Benson (from Oslo, Norway), revealed the existence of two different kinds of terpenoids (lipid & glycoside) in latex from the stem of E resinifera. A sequence of extractions, including 95% boiling ethanol and boiling water following boiling, were used to create the latex. Hergenhahn et al. found four terpenoids are: pro resinifera toxin, 12-deoxy-phorbol-13-isobutyrate, resiniferonol and 12-deoxy-phorbol-13-angelate, from a moisture removed methanolic extract of the newly harvested latexfrom Rabat (Morocco) containing E. resinifera. Two more terpenes, ingenol-3-acylates, and 12-deoxyphorbol-13-ester-20-acetates were isolated from E. resinifera latex that was obtained from Rabat by Hergenhahn et al. The latex extraction from aerial portion of E. resinifera was determined to have the richest chemical, ingenol, with a concentration of 16.71 µg/mL, according to a study conducted using an HPLC technique (Girin et al.). NMR was utilised in 2002 by Fattorusso et al. to examine the composition of latex derived from E. resinifera (Italy). The two terpenoids they found are called euphorbio sides A and B. The main triterpene that was isolated from E. resinifera latex was lanosta-8,24-dien-3β-ol.

Using cutting-edge analytical methods, several terpenoids have been discovered and isolated from Euphorbia species over the years. While Farah et al. used HPLC to identify euphorbioside from E. resinifera latex, Mallon et al. used LC-MS to identify euphol and euphorbol. Using 2D NMR, IR, UV, 1D, and HR-ESI-MS techniques, Wang et al. identified nine new triterpenes (three tirucallane and six euphane triterpenes) from Euphorbium. Ten triterpenes were extracted from E. resinifera latex two years later by Wang et al. utilizing semi-preparative HPLC and additional chromatographic methods. Using 2D NMR spectroscopy, (Zhao et al.: Identification of Ingol and Rhamnofolane Diterpenoids) isolated 18 diterpenoids from dried E. resinifera latex, including newly discovered euphorblin O (rhamnofolane diterpenoid) and 14 new in gol-type euphorblins A-N(diterpenoids). Later, two new triterpenes, euphorol J and euphorol K, as well as a well-known substance, kansuinone, were isolated by Wang et al. Additionally, they extracted two novel ingol-type diterpenes from E. resinifera latex in 2019: euphoresin A and B and euphatexol A and euphatexolB. These two uncommon euphane triterpenoids had their structures clarified by spectroscopic data (Qi et al.).

(Zhaoetal.:Tennewnortriterpenesfrom Euphorbia resinifera) identified 10 novel nor triterpenes (euphorbiumrins A–J) from E. resiniferafrom Urumqi (China) using the spectroscopic methods (IR, 2D NMR,1D, UV, HRESIMS). El Alami et al. identified two novel 16-diesters and12-Deoxy-16-hydroxyphorbol 13 using latex of E. resinifera from Beni Mellal (Morocco) in the same year using Ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry. Ourhzif et al. extracted Euphorbioside C (euphorbioside monohydrate) from the latex of this plant (Azilal, Morocco) using X-radiation crystallography, LC/HRMS NMR, and IR. Li et al. isolated five novel triterpenoids (euphatexols C–G) and four new lanostane triterpenoids from the ethanol extract of E. resinifera using IR, HRMS, and NMR methods. Moreover, Li et al. isolated seven triterpenoids from E. resinifera usingnormal-phase silica gel column chromatography, semi-preparative HPLC and ODS column chromatography.

Honey Composition

Honey has been utilized for a long period of time in traditional medicine to cure a variety of conditions, such as ulcers and cataracts, as well as burns and wound healing. Ash, pH, conductivity of electricity, free lactone, moisture content, water activity, and overall acidity are examples of physicochemical properties. Contamination (heavy

metals and pesticides) of honey has been investigated by scientists from a variety of scientific disciplines (Goldblum and Curtis; Malika et al.).

Three Moroccan Euphorbia honey samples were examined by Malika et al., who also assessed the samples' pH level, physicochemical properties, and microbiological features. A low amount of fungus, variance in lactone acidity, free acidity, and total acidity, and a water activity of 0.55 were all seen in the data. The standard plate count (SPC) of the samples ranged from 20 to 200 cfu/g. In this same setting, 29 samples of E. resinifera honey from the Moroccan provinces of Beni Mellal and Azilal were examined physicochemically (Moujanni et al.). Because most honeys had a low water content, they displayed good maturity. Conductivity, total acidity, ash, and hydroxymethyl furfural were reported to have average values of 1.6 g/kg, 3.6 mg/Kg,8 meq/kg, and451 µS/cm, respectively, by the authors. Mineral analysis revealed that honey has different concentrations of magnesium, calcium, phosphorus, sodium, silicon and sulphur, with high concentration of potassium element.

In recent research, Terrab et al. examined the geographic and palynological characteristics of the 29 samples from E. resinifera honey that were dispersed over a Middle Atlas Mountains (Morocco) Protected Geographical Indication (PGI) region (Goldblum and Curtis). Low quantities of pollen were found in the quantitative pollen analysis of the honey (average NPG (number of pollen grains) = 1490 per gram of honey), but there were also low levels of honeydew components (range from 0 - 95/g honey).

Bees will collect three things from the environment: pollen, honeydew, and water. All of them include natural components and toxins that are harmful to the public's health. One possible use for bee honey is as a biological indicator of environmental contamination. Moujanni et al. examined the presence of heavy metals and 202 pesticide residues in honey using a range of methods. The amounts of metal and pesticide contamination found in all the samples were found to be below predefined standards.

Pharmacological Investigation

E. resinifera is a significant traditional medicinal plant that Moroccans utilise to treat a variety of illnesses. Numerous additional pharmacological actions are included in the literature, including those that are antibacterial, anti-inflammatory,antioxidant, antileishmanial, antitumoural, immunomodulatory, antitrypanosomal, and insecticidal (Figure 2) (Hmidouche et al.).

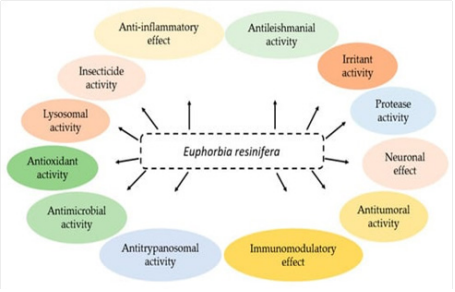


Figure 2 Biological properties of E. Resinifera (Oumaima)

Antimicrobial Activity

Antifungal Activity

There is just one research that describes about E. resinifera extract's antifungal activity, and that investigation was carried out by Benmehdi et al. averse to two different fungal strains. The antifungal efficacy of E. resinifera water-soluble extract was assessed by Benmehdi et al. using the proportion of radial development on solid media. They demonstrated that two fungus species, Penicillium expansum, and Aspergillus flavus that are hazardous to humans in varying amounts and had their mycelium growth inhibited by this extract. According to the findings, the mycelial growth suppression rates for A. flavus and P. expansum varied from 64.14% to 85.51% and 60.14% to 85.51%, respectively. On the one hand, E. resinifera extract's strong antifungal action highlights the impact of bioactive components; hence, more studies should be carried out to determine how different chemical classes affect different fungal strains. Research on extracts' ability to neutralise different types of fungal pathogens, however, is lacking. To avoid contamination, it is therefore important to investigate E. resinifera extracts, honey and chemical classes against different pathogenic fungal strains. To produce an antifungal medication,

comprehensive research (including in vivo, in vitro, and preclinical testing (in vivo)) should be carried out.

Antibacterial Activity

Numerous investigations have evaluated the antimicrobial characteristics of E. resinifera honey and the antimicrobial efficacy of various extract fractions. A number of component extracts were evaluated; they included aerial sections, latex, roots, flowers, and stems. In addition, the method most frequently employed to estimate the antibacterial activity by microdilution test.

An aqueous extract of E. resinifera from Naama,demonstrated antibacterial activity against E. coli, according to Benmahdi et al. According to Farah et al., the most potent extract was ethyl acetate, which was obtained from E. resinifera roots (Damnat, Morocco). The extracts were found to be most effective against E. coli (MICs 1.0–1.5 mg/mL) and least effective against S. typhimurium (MICs 1.5–2.0 mg/mL). Ethyl acetate and methanolic extracts of the flowers,roots, and stems of E. resinifera from Beni Mellal (Morocco) were found to be active against S. aureus and B. subtilis in a study by Farah et al. . The roots displayed the highest potential. Additionally, they tested the euphorbioside from E. resinifera latex and found that the antibacterial activity was only present in semi-synthetic versions. According to Talbaoui et al., Rhodococcus sp. GK1 (15 mm) and R. equi (18 mm) were inhibited by dichloromethane extracts from E. resinifera's aerial portion (Kuehn).

The highest energy dense food found in the nature is honey, which is also high in sugars like glucose and fructose, traces of vital vitamins & minerals, and has significant medicinal benefits (Abderrahim et al.). Euphorbia honey has long been used in Mediterranean nations to treat conditions like digestive, metabolic, and circulatory issues (Alami et al.). In 2020, Bendjamaa et al. used a well agar diffusion assay to assess the effect (antibacterial) of E. resinifera honey against E. coli and S. aureus. They discovered that at 50% (v/v) dilution, all honey samples inhibited bacterial growth, with inhibition zones measuring 13.84 ± 1.10 mm for E. coli and 25.98 ± 0.11 mm for S. aureus. E. resinifera honey may be a natural treatment for diseases caused by pathogens due to its pH, phytochemical properties, viscosity, and H_2O_2 content, and meets bacteriological standards, excluding coliforms, Clostridium perfringens, and Salmonella spp (Moujanni et al.). The varying findings in this research can be attributed to differences in extract type, plant part, location, experimental design, extraction techniques, and bioactive chemicals (Bouyahya et al.; El Idrissi et al; Khouchlaa et al., 2021). Even though E. resinifera exhibits strong antibacterial properties in vitro, more in vivo and clinical research is required.

Antioxidant Activity

Natural antioxidants in E. resinifera have been the subject of numerous investigations, with a particular emphasis on the antioxidant capacity of diverse extracts derived from distinct plant sections (Benmehdi et al.; Hanane et al.). The main assays employed in these investigations were DPPH, superoxide, and nitric oxide. The ability of Benmehdi et al. to donate hydrogen was demonstrated by the antioxidant activities of methanol, flavonoid, and alkaloid extracts of aerial portions from E. resinifera (Algeria), with IC50 values of 0.0086 mg/mL, 0.378 mg/mL, and 1.171 mg/mL, respectively. Hanane et al. evaluated the antioxidant impact of root extracts from E. resinifera (Morocco), finding that the extract with the highest potency was ethyl acetate, with a SC50 value of 18.20 ± 0.41 µg/mL; extracts with intermediate activity included acetone, ethanol, and dichloromethane. Anti-DPPH activity and phenolic content were correlated, with the methanolic extract of roots showing stronger antioxidant activity (10.01 µg/mL) than ethyl acetate (18.85 ± 0.12 µg/mL). The antioxidant capacity of E. resinifera honey and aqueous extracts was evaluated by Boutoub et al. who discovered an anti-DPPH effect with an IC50 of 80.1 ± 1.1 mg/mL, superoxide activity ofnitric oxide radical effect of 88.2 ± 0.8 mg/mL and 3.70 ± 0.0 mg/mL. Climate, botanical origin, phenolic content, and type of extract are among the variables that can cause variations in scavenging activity (Benjamaa et al.; Sousa et al.). It is important to take into account the compounds' synergistic effects as well as the need to evaluate latex and additional E. resinifera components.

Antitumoral Activity

Only aerial parts of E. resinifera were studied for their antitumoral properties in one study (Talbaoui et al.). In this study, dichloromethane and methanol extracts were tested for cytotoxicity on cancer cell lines; Kidney epithelial cells from African green monkey (Vero); RD (rhabdosarcoma rat), and BSR. They were highly cytotoxic to BSR cells with an IC50 of 77.2 µg/mL and demonstrated potent anticancer activity and t full suppression potential. Even though slight components might be playing their roles through an additive or synergistic effect, people should take this action as a point to indicate the principal compounds in these extracts were mainly contributing towards it (Talbaoui et al.; El Idrissiet al.). Although for thousands of years E. resinifera was treated as a method against cancer, its global anticancer activities are not so well-documented. Further research work is needed to determine how the various parts of this plant can influence different types of cancer.

Anti-Inflammatory Effect

Nitric oxide (NO), a free radical, has been shown in recent years to have a strong cytotoxic impact and to have a role in the aetiology of several human illnesses. Researchers focused their study on neutralising NO in this particular situation (Engwa). Li et al. looked into and evaluated the anti-inflammatory qualities of five triterpenoids that were separated and discovered from E. resinifera latex. The study used an assay for nitric oxide production decrease to assess the anti-inflammatory activity of euphatexols C-G and E on RAW264.7 cells. While euphatexol E inhibited NO creation with 21.89 µM IC50 value, comparable to the beneficial control (dexamethasone), euphatexols C–G dramatically reduced NO production (Li et al.). Strong anti-inflammatory effects were demonstrated by these compounds, but additional in vivo research is required to evaluate their efficacy and safety.

Antileishmanial Activity

An endemic illness called leishmaniasis is brought on byover 20 species of protozoan parasites, transmitted by sandfly species. It has three main forms: visceral, cutaneous, and mucocutaneous. Due to side effects and drug resistance, limited drugs are available (Samaranayake et al.). Potential therapeutic agents have been found as natural chemicals and medicinal plants. According to research, leishmaniasis might be prevented by using medicinal herbs (Bahmani et al.). Twelve semisynthetic terpenoid derivatives made by chemically modifying E. resinifera were reported to exhibit strong antiparasitic efficacy against promastigotes of Leishmania infantum by Mazoir et al. The most cytotoxic compounds were24-dien-7,11-dione, 24-dien-11-one, 3β-Tosyloxy-24-methylen-elemo-lanosta-8 and 3β-Tosyloxy-24-methylen-elemo-lanosta-8. Chinese hamster ovary cells were less cytotoxic than those of other mammals. Mazoir et al. hypothesised that the use of triterpenes may disrupt sterol metabolism, as Leishmania parasites rely on particular Indigenous sterols for development and survival (Benjamaa et al.).

Antitrypanosomal Activity

Natural compounds and medicinal plants have been recognised as potential therapeutic agents. Research suggests that taking medicinal herbs may help prevent leishmaniasis (Bahmani et al.). Mazoir et al. found that twelve semisynthetic terpenoid derivatives produced by chemically altering E. resinifera showed high antiparasitic activity against promastigotes of Leishmania infantum. The most cytotoxic compounds were 3β-Tosyloxy-24-methylen-elemo-lanosta-8,24-dien-11-one and 3β-Tosyloxy-24-methylen-elemo-lanosta-8,24-dien-7,11-dione. Chinese hamster ovary cells were less cytotoxic than those of other mammals. Mazoir et al. hypothesised that the use of triterpenes may disrupt sterol metabolism, as Leishmania parasites rely on particular endogenous sterols for development and survival (Benjamaa et al.).

Protease Activity

Since plant proteases obstruct blood coagulation and antiplatelet action, they constitute a significant source of antithrombotic medicines. In 2020, Siritapetawee et al. conducted research to examine the impact of pure protease derived from E. resinifera latex on the blood coagulation system and human platelet function. The naturally occurring inhibitors antithrombin III and α2-macroglobulin did not block

the purified protease. All fibrin clot chains were hydrolysed by the enzyme at doses greater than 0.5 μM. PT (Prothrombin time) and APTT (activated partial thromboplastin time) tests also revealed anticoagulant action. According to Siritapetawee et al., the purified protease was nontoxic to the four main blood groups of human red blood cells and human peripheral blood mononuclear cells and reduced the accumulation of platelets activity in a dose-dependent manner. These findings suggest that the purified protease from E. resinifera latex may find application in the management of thrombosis. Similarly, Siritapetawee et al. isolated serine protease from E. resinifera latex and examined it's biochemical characteristics against fibrinogenolytic activity with substrate as human fibrinogen in a prior work. According to that study, serine protease could cleave human fibrinogen under ideal circumstances at 45 °C and pH 5.0. It also demonstrated a broad stability of pH range of 1–14 and a resistance to denaturation at 65–66 °C. The pure protease from E. resinifera latex showed less efficacy in separating human fibrinogen than human plasmin, indicating possible applications in thrombosis prevention and therapy.

Antilipoxygenase, Anti-Xanthine Oxidase, Antityrosinase and Antiacetycholinesterase Activities

One useful treatment approach is to investigate the enzymes that are necessary for inhibition. Enzymes that are significant for pharmacology and physiology include tyrosinase, lipoxygenase, acetylcholinesterase, and xanthine oxidase. Approximately 47% of all medications on the market are thought to have this as their main target, blocking various enzymes. Accordingly, one of the main areas of focus for pharmacological research and pharmaceuticalis the development of novel, highly effective enzyme inhibitors (Gulati et al.). The genus Euphorbia has demonstrated the inhibitory impact of a broad variety of enzymes. The effects of E. resinifera aqueous extracts and honey on the enzymes lipoxygenase, acetylcholinesterase, xanthine oxidation, and tyrosinase were compared by Boutoub et al. (Hanane et al.). First, the ability of E. resinifera water-soluble extracts to inhibit four enzymatic activities was examined. After two hours of extraction, the aqueous extract at three distinct ratios 1:50,1:20 and 1:100 was produced. The aqueous extract at a 1:100 ratio clearly inhibited xanthine oxidase more effectively than all other ratios (IC50 = 26.1 mg/mL). The highest antilipoxygenase activity (IC50 = 0.99 mg/mL) was seen in the same ratio from the E. resinifera aqueous extract after one hour of extraction. Research has demonstrated that the water-soluble extract of Euphorbia resinifera outperformed Euphorbia officinarum in terms of activity, regardless of the ratio or duration of extraction. The study found that aqueous extracts from E. resinifera and E. officinarum honey showed improved activity for tyrosinase at a 1:100 extraction ratio. However, the inhibitory activities of E. resinifera's honey were less than those of E. officinarum's honey, which showed higher IC50 values on lipoxygenase, xanthine oxidase, tyrosinase, and acetylcholinesterase. The aqueous extracts and honey samples demonstrated potential as strong enzyme inhibitors, potentially used as medicinal agents to treat various illnesses.

Neuronal Effect

Brain injury and permanent neuronal loss are caused by neurological illnesses, vascular disorders, and acute traumas. This results in motor dysfunction, cognitive disability, and personality abnormalities. Neural stem cells (NSCs) in the hippocampus's dentate gyrus (DG) and subventricular zone (SVZ) allow the brain to produce new neurones; nevertheless, neuronal regeneration in injured brain areas is uncommon. Therefore, it is imperative to search for chemicals that enhance neural stem cell (NSC) capacity to generate new neurones in injured brain areas, therefore promoting functional recovery. The peripheral terminals of sensory neurones include a sensor called the vanilloid receptor subtype 1 (VR1) that responds to unpleasant stimuli. Its expression in non-neuronal tissues and other brain nuclei puts it to a wider clinical condition than the perception of pain and raises the possibility of unanticipated adverse effects, especially with term vanilloid exposure (Szallasi). Capsaicin and unpleasant heat regulate this receptor, VR1, and when it is activated, pro-inflammatory peptides are released and attach to the genecalcitonin (CGRP),

causing peripheral and hyperalgesia sensitisation (Basu et al.). Strong agonists that block VR1, such capsaicin and resiniferatoxin, which are taken through the latex of E. resinifera, cause desensitisation of VR1 and ablation of nociceptors that express VR1, hence producing peripheral analgesia. When the afferent branch of the nullifying reflex is impaired, they are useful for detrusor hyperreflexia and excessive bladder activity (Basu et al.).

Resiniferatoxin, produced from E. resinifera, was discovered by the researchers at NIH (National Institutes of Health) Clinical Centre to reduce rats' discomfort after surgery. It is chemically comparable to capsaicin and is five hundred times more effective than capsaicin. It can disrupt pain-related transmission in nerve cells and reduce pain-related behaviours in rats with incised paws (Kuehn). Recent research has shown that phorbol, an ester of polyhydroxylated tetracyclic diterpene, and its derivatives, especially 12-deoxy phorbol (DPB), can stimulate neurogenesis in the brain and spinal cord, activating protein kinase C (PKC) and promoting the proliferation of neural progenitor cells (NPCs). This has been demonstrated to enhance memory and learning in mice through the production of TGFα and the growth of NSCs (Benjamaa et al.). Two novel 16-diesters and 12-deoxy-16-hydroxyphorbol 13were derived from the E. resinifera latex in 2021. These compounds promote TGFα release in a typical PKC-dependent way, increasing stimulating neurogenesis and NPCs proliferation. Opioid-based medications are a vital component of pain management, and pain treatment can be enhanced by finding effective non-opioid substitutes and to prevent side effects focusing on the peripheral nervous system.

Immunomodulatory Effect

By examining E. resinifera's immunomodulatory activities in vitro, Kreher et al. Eleven triterpenes, twoingolesters, and three 12-deoxyphorbol esters were discovered from the chemicals determined by MS and HPLC from E. resinifera latex. In vitro, only 12-deoxyphorbol esters stimulated the growth of lymphocytes; triterpenes and ingol esters did not exhibit any immunomodulatory effects. Issiki et al. used young male mice to investigate the immunomodulatory function of E. resinifera in vivo (Zissu). In the study, acute and sub-acute toxicity tests were conducted using an aqueous extract of E. resinifera aerial parts at varying doses. The group that did not receive a hazardous dosage had a substantial increase in DTH reactivity response and antibody titer values. A greater number of lymphocyte infiltrates in the tissues under investigation may result from the high terpenoid content in E. resinifera acting as an immunomodulatory agent.

Irritant Activity

The irritating properties of latex and E. resinifera resin were investigated in vivo on a mouse's ear by Hergenhahn et al. Esters of the polyfunctional diterpenes - ingenol, 12-deoxyphorbol, 12,20-dideoxyphorbol,12-deoxy-16-hydroxyphorbol,and ingenol - were purified and then chemically characterised using resiniferonol and resin. The irritating effects of these compounds were measured in irritation units. According to Hergenhahn et al., two ingenol esters did not irritate the ears of mice. Two 12,20-dideoxyphorbol esters also showed very little irritation. On the other hand, the irritating properties of resiniferonol, 12-deoxy-16-hydroxyphorbol, and 12-deoxyphorbol differed. Similarly to Furst, Zayed et al. extracted 2 ester compounds (3-monoesters and 13,20-diesters) from the E. resinifera resin and investigated how irritating they were to a mouse ear in vivo. Generally speaking, the 13,20-diesters exhibit less irritating action than their comparable 13-monoesters. According to the scientists, the 13-monoesters' acyl chain length has a significant impact on their irritating action.

Lysosomal Activity

The study investigated the effectiveness of Euphorblin D and Euphorblin B, which are produced from the latex of E. resinifera, in increasing lysosomal production using the HeLa cell line. At various times, these substances were tried at various doses (Mohamed). Tracker Lyso To examine lysosome induction, red staining was utilised. The majority of isolated chemicals made the staining more intense. After three hours of treatment with several doses, HeLa cells showed the most rise at 60 μM. Different reports of an induction impact on lysosomal production have demonstrated that

isolated diterpenoids from E. resinifera latex can stimulate lysosome biosynthesis (Mohamed).

Toxic Effect

Although E. resinifera extract has a wide range of pharmacological properties, nothing is known regarding its toxicity. Given its propensity for intoxication, latex is not recommended for use in traditional folk medicine or external medical applications. In tumour-promoting tests, Hergenhahn et al. pointed out and examined the diterpene esters that function as tumour promoters. According to the study, homologous stimulator mix RL 13 is ten times more potent than the conventional tumour promoter TPA (12-0-tetradecanoylphorbol-13-acetate). According to Zayed et al., tetradecanoate and octadecanoate were comparable to TPA at specific dosages, whereas 13-monoesters were inert at certain concentrations. It was previously discovered that 13-tetradecanoate was just as potent as TPA. Therre et al. examined the chemoprotective and DNA-damaging properties of E. resinifera. Using two standardised assays, the study examined the genotoxicity of complex combinations of ethanolic extracts on human hepatoma cells. The extracts underwent single-cell gel electrophoresis comparison with the standard mutagen, benzo[a] pyrene. Strong cytotoxic effects were demonstrated by E. resinifera up to dilution D4. Therre and colleagues discovered that diterpene esters and pharmaceuticals had no bearing on cogenotoxic effects. But for some reason, the benzo[a]pyrene-induced DNA damage was significantly amplified by 12-O-tetradecanoylphorbol-13-acetate. Following an investigation, Li et al. found no cytotoxic impact at 10 µL for the euphatexols C–G from E. resinifera latex.

With juvenile adult male mice, the toxic impact of E. resinifera was investigated in vivo (Zissu). The aqueous extract was given orally in different dosages for toxicity studies that were both acute and subacute. Kidney activity was not different in the treatment or control groups, according to biochemical tests. On the other hand, notable dose-dependent increases in ALAT and ASAT were noted at higher dosages. Histopathological analysis revealed no discernible differences between treated and control mice's kidney or spleen tissues. To establish the safe dose of E. resinifera, these results emphasise the necessity of more preclinical research, particularly in vivo investigations.

Insecticide Activity

To control the insect problem, some researchers focused their study on the usage of chemicals derived from triterpenes. Smaili et al. studied the effects of the four semisynthesized triterpene derivatives on E. resinifera latex (Morocco). They found that at doses of 500 and 100 mg/mL, these triterpenes prevented tomato seed sprouting, but less pronounced at concentrations of 50 and 10 mg/mL. They also created resistance to Verticillium wilt, reducing symptoms at doses lowered to 10 mg/mL.

Clinical Trials

The clinical activity and safety of E. resinifera compounds and extracts were tested in patient clinical trials to examine their potential for treating various diseases such as cervical ripening, asthma, labor stimulation, verrucae, pain relief and corneal oedema (Farah et al.; Kuehn; Renukadevi et al.; Sultana et al.).

In 1953, 60 patients affected by verrucae plantares were treated by Goldblum and Curtis using a 30% alcoholic solution of E. resinifera. Adhesive tape was used to seal the solution onto the core keratotic region of the verruca (Farah et al.). The wart was re-clipped and Euphorbium was reapplied after 48 hours. After 4 months of follow-up period, verrucae disappeared in all but two of the patients. The authors proposed that the elimination of verrucae was caused by lysing dermis collagen and rete mucosum cells (Goldblum and Curtis). Nonetheless, more research on the effectiveness of terpenoids as a treatment for verrucae has to be done.

Zissu examined a case report of a patient who had experienced an eight-day post-influenza asthma attack and had developed new symptoms, including a greenish mucus from nasal passages, and candidiasis from his mother and sister, along with jealousy and aggression towards the latter (Renukadevi et al.). This was just done for a clinical trial for asthma studies. The patient was treated with Antimoniumtartaricum and E. resinifera 7CH daily,

along with standard weekly treatments like sulfur and psorinum. After a second consultation, there was a noticeable improvement and no signs of respiratory allergies or high temperature.

Sultana et al. assessed the efficacy of the Unani herb formulation in inducing labour and cervical maturation in 38 expectant mothers. Oral administration of the polyherb Unani and a vaginal pessary containing borax, Gossypium herbaceaum, and E. resinifera were administered to the patients. Between induction and delivery, the average time was 12.3 ± 4.7 hours. Of the 38 women, 84.2% gave birth on their own, 7.8% vaginally following an injection of oxytocin or cerviprime, and 7.8% by caesarean. Antibacterial and antioxidant qualities were demonstrated by E. resinifera, and the polyherbal compound had positive benefits without negative side effects.

This study looked at how propolisfeom honey oil extraction of E. resinifera affected the blood glutamate transaminase concentrations in people with chronic hepatitis C.Utilising olive oil, the extract was made and combined with either multi-floral honey or E. resinifera honey for patients without diabetes. Before meals, the extract was taken orally three times an hour. Findings indicated that all patients, even those who had not responded to traditional therapy, had improved liver function, substantial drops in SGPT and SGOT concentrations, and suppression of tiredness symptoms. According to Zayed et al., propolis honey oil extract from E. resinifera strengthened the benefits of apitherapy for patients with chronic hepatitis and restored normal liver function.

About the study of pain management, Kuehn reported that compounds derived from Moroccan E. resinifera cactus plants effectively mitigate postoperative pain in rats, as demonstrated by studies conducted at the NIH (National Institutes of Health) Clinical Centre (Goldblum and Curtis). To evaluate the effects of injectable resinifera toxin upon the brain and spinal cord, the NIH Clinical Centre conducted a phase I clinical investigation. According to this study, training did not affect nerve cell signalling and the discomfort was connected.

Mancera and Wadia recently used E. resinifera resin to explain the onset and remission of corneal oedema in a patient (Kuehn). Following therapy with resinifera toxin and stopping the interfering medication, ocular oedema progressively went away and visual acuity restored to normal.

Conclusion

We gathered information on E. resinifera by searching many scientific databases including , Scopus, Springer Link, PubMed, Web of Science, Wiley Online, SciFinder, and Google Scholar. This section discusses research on the anticancer, anti-inflammatory, antiprotease, antileishmanial, immunomodulatory, lysosomal properties, and irritating of E. resinifera or its bioactive components. We extensively analysed and reviewed earlier studies on E. resinifera in this review, including their taxonomy, botanical description, geographic distribution, and therapeutic applications. Furthermore, reports on pharmacological effects, toxicity, and bioactive substances were made. Processes based on biological data justify the utilisation of E. resinifera in traditional medicine. Further comprehensive investigation is required to elucidate the pharmacological processes and demonstrate the safety and effectiveness of E. resinifera latex extracts and related constituents furthermore, investigations to elucidate the molecular mechanisms underlying its pharmacological actions. Additionally, rigorous studies on the pharmacokinetics and pharmacodynamics of its extracts and compounds are essential to understanding their behavior in biological systems better.

Future research should focus on isolating and characterizing novel bioactive compounds from E. resinifera, and assessing their efficacy in preclinical and clinical settings. Special attention should be given to developing targeted therapies, such as anticancer drugs, based on their potent bioactive constituents. Investigations into safe dosage forms, potential side effects, and long-term safety profiles are crucial for advancing its role in drug development and therapeutic applications.

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