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EUPHORBIA RESINIFERA AND TRADITIONAL MEDICINE

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ABSTRACT

Euphorbia resinifera (Zaggûm or Tikiut) is an endemic species of Morocco, predominantly found in the Middle Atlas Mountains, and has long been used in traditional medicine for the treatment of various diseases, particularly cancer. This review aims to critically analyze and synthesize existing knowledge on *E. resinifera*, including its botanical characterization, taxonomy, geographical distribution, and traditional medicinal applications, as well as its bioactive compounds, toxicological aspects, and pharmacological properties. A comprehensive literature search was conducted using major scientific databases such as Scopus, PubMed, Web of Science, SpringerLink, SciFinder, Wiley Online Library, and Google Scholar, focusing on studies involving *E. resinifera* and its bioactive compounds, particularly those addressing antitumor, anti-inflammatory, antileishmanial, antiprotease, immunomodulatory, irritant, and lysosomal activities. The available evidence indicates that *E. resinifera* latex, honey and propolis are widely used in Moroccan folk medicine to treat conditions such as diabetes, cancer, inflammatory skin disorders, and wounds. Phytochemical investigations have identified a range of bioactive compounds, especially terpenoids, while *in vitro* and *in vivo* studies demonstrate that latex extracts and isolated compounds exhibit diverse biological activities, including antioxidant, antimicrobial, antitumor, anti-inflammatory, antileishmanial, immunomodulatory, and neuroprotective effects. The traditional use of *E. resinifera* honey and its propolis is supported by emerging strong biological evidence, with safety and efficacy, as a functional food, that also may have a phyto-adaptogenic role potential as an adjuvant complementary to treatment of Tuberculosis. While also they act stimulating cicatrization of ulcers with torpid evolution, being possible candidates to be used in Cutaneous Leishmaniasis and Hanseniasis lesions. There’s a potential role in biotechnological environmental researches, but also to translational investigations much needed to global contemporary public health.

Keywords: *Euphorbia resinifera* honey and propolis, Traditional Medicine, Cancer, Neglected Diseases, lisossome scavenger activities.

RESUMO

Euphorbia resinifera (Zaggûm ou Tikiut) é uma espécie endêmica de Marrocos, encontrada predominantemente nas montanhas do Médio Atlas, e tem sido utilizada há muito tempo na medicina tradicional para o tratamento de diversas doenças, particularmente o câncer. Esta revisão tem como objetivo analisar criticamente e sintetizar o conhecimento existente sobre E. resinifera, incluindo sua caracterização botânica, taxonomia, distribuição geográfica e aplicações medicinais tradicionais, bem como seus compostos bioativos, aspectos toxicológicos e propriedades farmacológicas. Uma busca bibliográfica abrangente foi realizada utilizando as principais bases de dados científicas, como Scopus, PubMed, Web of Science, SpringerLink, SciFinder, Wiley Online Library e Google Scholar, com foco em estudos envolvendo E. resinifera e seus compostos bioativos, particularmente aqueles que abordam atividades antitumorais, anti-inflamatórias, antileishmania, antiprotease, imunomoduladoras, irritantes e lisossômicas. As evidências disponíveis indicam que o látex, o mel e o própolis de *E. resinifera* são amplamente utilizados na medicina popular marroquina para tratar doenças como diabetes, câncer, distúrbios inflamatórios da pele e feridas. Investigações fitoquímicas identificaram uma gama de

compostos bioativos, especialmente terpenoides, enquanto estudos *in vitro* e *in vivo* demonstram que os extratos de látex e os compostos isolados exibem diversas atividades biológicas, incluindo efeitos antioxidantes, antimicrobianos, antitumorais, anti-inflamatórios, antileishmania, imunomoduladores e neuroprotetores. O uso tradicional do mel e do própolis de *E. resinifera* é sustentado por fortes evidências biológicas emergentes, com segurança e eficácia, como alimento funcional, que também pode ter potencial fitoadaptogênico como adjuvante complementar ao tratamento da tuberculose. Além disso, atuam estimulando a cicatrização de úlceras com evolução lenta, sendo possíveis candidatos para uso em lesões de leishmaniose cutânea e hanseníase. Há um papel potencial em pesquisas biotecnológicas ambientais, bem como em investigações translacionais muito necessárias para a saúde pública global contemporânea.

Palavras-chave: Mel de Euphorbia resinifera e própolis, Medicina Tradicional, Câncer, Doenças Negligenciadas, atividades de eliminação de toxinas por lisossomos.

BACKGROUND

The Euphorbiaceae family comprises approximately 8,000 species, of which nearly 2,000 are laticiferous, including several members of the *Euphorbia* genus. Plant species have been used for centuries in ethnomedicine, transmitted orally, as well as in traditional medicine systems documented in written form. In recent decades, species of the *Euphorbia* genus have been extensively investigated due to the chemical complexity of their latex and the presence of bioactive compounds with both economic and pharmacological relevance (Mwyne; Van Damme, 2011; Chen et al., 2015; Salehi et al., 2019).

Phytochemical analyses of *Euphorbia resinifera* have identified compounds such as ingenol esters, a class of immunomodulatory diterpenes capable of inducing apoptosis in malignant cells (Girin et al., 1993, cited in Zissu et al., 2011). It is well established that species within the same genus often share similar chemical structures and biological activities (Archanjo et al., 2016; Azizi et al., 2021).

Euphorbium is a medicinal product derived from the latex of *E. resinifera*, also originates from traditional medicine practices (Sultana et al., 2015; Wang et al., 2018) and is currently used worldwide in oncology contexts, being commercially available in pharmaceutical markets. Toxicological and preclinical studies have been conducted (Lata;

Saxena, 2003; Saad et al., 2006; Ernst et al., 2015; Chen et al., 2015; Salehi et al., 2019), and clinical trials, including those registered by the NIH, have investigated its use in the management of severe cancer-related pain (ClinicalTrials.gov).

Given the broad biotechnological potential demonstrated by this species and supported by approximately 25 years of consistent scientific publications documenting its use in traditional medicine, an important question emerges: what is currently known from a scientific perspective about *E. resinifera* latex and honey? In this context, the present study aims to describe the traditional medicinal uses of *Euphorbia resinifera*.

METHODOLOGY

This study consists of a bibliographic review focused on the traditional medicinal uses of *Euphorbia resinifera*. A comprehensive literature search was conducted using scientific databases and digital platforms to identify relevant publications addressing the ethnomedicinal applications, pharmacological properties, and clinical evidence associated with this species. Additionally, an exploratory query was performed using the Consensus AI platform (https://consensus.app/search/ha-relatos-da-aplicacao-clinica-da-euphorbia-resin/n6RSH6BJSdeYJvsJKK7t-A/?utm_source=share&utm_medium=clipboard) to investigate the existence of reported clinical applications of *Euphorbia resinifera*. The retrieved information was screened, analyzed, and synthesized to provide an integrative overview of the current scientific knowledge regarding its traditional use and therapeutic potential.

RESULTS

The results of this review were based on the analysis of current scientific literature addressing the traditional medicinal use, phytochemistry, pharmacology, and clinical evidence related to *E. resinifera* latex and honey.

COMPREHENSIVE STUDY ON PLANT BIOTECHNOLOGY

Plant biotechnology refers to the application of scientific techniques, such as genetic engineering and plant tissue culture, to modify, propagate, or improve plants for specific traits, including increased productivity and enhanced production of bioactive compounds. A comprehensive study involves an in-depth and systematic investigation that integrates multiple perspectives, methodologies, and sources of information, aiming to provide a complete understanding of a given subject. In this context, the study of *E. resinifera* requires the integration of phytochemical, pharmacological, and biotechnological approaches to fully elucidate its therapeutic potential.

Botanical Description and Ecophisiological Aspects

The Euphorbiaceae family comprises more than 300 genera and approximately 8,000 species, including numerous laticiferous plants within the *Euphorbia* genus. This genus includes *Euphorbia resinifera*, commonly referred to as Euphorbia resin or Euphorbium, classified as dicotyledonous species (Webster, 1994; Mwyne; Van Damme, 2011; Terrab et al., 2022; Bruyns; Klak; Hanáček, 2011; Hmidouche et al., 2023).

Euphorbia resinifera O. Berg & C.F. Schmidt is an endemic species of Morocco, first described by Vindt (1953). It is predominantly distributed in the central regions of the country, particularly in Azilal and Beni Mellal, within the Middle Atlas Mountain range. Its distribution is associated with a complex interplay of factors, including soil characteristics, paleogeography, and climatic conditions. From a bioclimatic perspective, the species occurs in environments ranging from arid to subhumid, including temperate, cool, and, in some cases, exceptionally cold variants (Terrab et al., 2022; Hmidouche et al., 2023).

This species plays a significant socioeconomic role in the regions where it occurs, particularly through the production of high-quality monofloral honey. Euphorbia honey from these areas has been granted Protected Geographical Indication (PGI) status, contributing to

the recognition of Azilal and Beni Mellal as important territories for honey production in the Mediterranean region. Locally, the plant is known by the Arabic name “Zaggoume.” (Terrab et al., 2022; Hmidouche et al., 2023).

Morphologically, *E. resinifera* is a perennial, leafless, cactus-like plant, typically reaching approximately 60 cm in height. It is characterized by four-sided, nearly square stems and short brown spines, features that contribute to its adaptation to harsh environmental conditions (Belakhdar, 1997; Benmehdi et al., 2013; Terrab et al., 2022; Hmidouche et al., 2023).

The native distribution is concentrated in Morocco (Atlas, Anti, Saharan, i.e., North Africa), with secondary records in cultivated areas on several continents. In Brazil, the species is mainly cultivated in botanical collections, research institutions, and private gardens, concentrated in the Southeast and Northeast regions (Sabri et al., 2023; Varricchio, 2024).

Phytochemical Aspects

Traditional extraction methods, such as infusion and maceration, are widely used in herbal preparations due to their simplicity, short processing time, and efficiency in yielding bioactive compounds (Benrahou et al., 2022). Phytochemical analyses have demonstrated that *E. resinifera* extracts, particularly ethanolic extracts, are rich in polyphenols and flavonoids. It is important to note that the composition and yield of these compounds can be significantly influenced by several factors, including extraction method, solvent type, extraction time and temperature, particle size of plant material, solvent-to-solid ratio, environmental conditions, and harvest period (Zayed; Sorg; Hecker, 1984).

Advanced analytical techniques, such as Electrospray Ionization High-Resolution Mass Spectrometry (ESI-HRMS), have enabled the identification of compounds such as saponarin in aqueous extracts (Benrahou et al., 2022). In addition, studies report that the latex of *E. resinifera* contains a wide variety of bioactive constituents, including triterpenoids, diterpenoids, and phenolic acids. Among these, euphane triterpenes, tirucallane triterpenes,

spirotriterpenoids, and nortriterpenes have been identified (Kabbaj et al., 2012 apud Benrahou et al., 2022). Overall, terpenoids represent the dominant class of phytocompounds in latex extracts (Hammad et al., 2025).

Classical studies demonstrated that certain diterpene esters, such as those related to phorbol derivatives, exhibit biological activity comparable to known tumor promoters like 12-O-tetradecanoylphorbol-13-acetate (TPA), although often requiring higher concentrations. Additionally, structural variations—particularly the length of acyl chains in these compounds—have been shown to significantly influence their irritant and biological activity. Long-chain esters tend to exhibit tumor-promoting effects, whereas short-chain derivatives are more commonly associated with cytotoxic activity. Ongoing research continues to identify new terpenoid structures, reinforcing the chemical diversity and pharmacological relevance of this species (Li et al., 2021; 2022 Hmidouche et al., 2023).

Honey derived from *E. resinifera* also represents an important phytochemical and therapeutic product. Traditionally used for centuries in the treatment of various conditions, Euphorbia honey has been reported to be beneficial in the management of cataracts, ulcers, burns, and wound healing (Wendling da Silva et al., 2025). Its physicochemical properties indicate high maturity, characterized by low water content, and a mineral composition rich in potassium, along with magnesium, calcium, phosphorus, sodium, silicon, and sulfur (Terrab et al., 2022).

Palynological and geographical studies conducted on *E. resinifera* honey samples from Protected Geographical Indication (PGI) regions of the Middle Atlas Mountains revealed relatively low pollen content (average number of pollen grains of approximately 1490 grains/g of honey) and low levels of honeydew elements. Importantly, analyses also demonstrated that pesticide residues and heavy metal concentrations remained below established safety limits, supporting the quality and safety of this product (Terrab et al., 2022).

Genus Euphorbia, have long been known to yield latexes and extracts with a wide range of therapeutic properties. They are also renowned for providing unifloral honey that is produced and commercialized mainly in the Mediterranean region and is much appreciated

owing to its medicinal properties. By better understanding the unique properties and potential uses of Euphorbia honey, also known as Daghmous, which is distinct in various aspects. Based on its pollen composition, it has a high content of pollen grains originating from Euphorbia spurge (minimum of 25% In Sahri et al., 2023).

This honey possesses a dark amber color, attributed to specific nectar sources, and chemical composition, and it's very rich in essential components like carbohydrates, proteins, phenolic compounds, and volatile organic compounds (VOCs). Euphorbia honey exhibits strong antioxidant and cytotoxic properties, suggesting its potential utility in medicine, cosmetics, and the food industry (Sahri et al., 2023).

Both aqueous and organic extracts of *E. resinifera* have been associated with diverse pharmacological properties. The latex, in particular, has long been used in traditional medicine; however, it is also known to cause frequent intoxications, which has restricted its application mainly to external uses and veterinary medicine. In this context, several studies have focused on the isolation and characterization of diterpene esters responsible for both biological activity and tumor-promoting effects (Hmidouche et al., 2023).

Ethnobotanical and Ethnomedicinal Use

E. resinifera is considered one of the oldest medicinal plants within Western traditional medicine and is widely used by Moroccan herbalists and traditional practitioners. Different parts of the plant—including stems, fruits, flowers, latex, and seeds—are employed in a variety of therapeutic applications. The stems, fruits, and flowers have traditionally been used to treat venomous bites, while latex mixed with hot water and honey is also commonly applied for snakebites and scorpion stings. A small drop of latex has been used topically for the treatment of warts, whereas stems (without latex or bark) and the milky sap have been used in the management of female genital cysts. Seed powder mixed with honey has been reported as a remedy for digestive disorders, and dried aerial parts combined with honey have been traditionally used to treat goiter (Cragg; Newman, 2005).

In addition, ground aerial parts mixed with honey—or honey alone—have been administered orally for the treatment of various types of cancer. Topical application of a small amount of latex has also been reported for the treatment of skin cancer. These practices are particularly documented among populations in regions such as Rabat (Cragg; Newman, 2005; Kabbaj et al., 2012).

The whole plant, whether fresh or dried, is traditionally recognized for its anti-inflammatory properties. Preparations combining warm water, honey, and latex are commonly used to treat skin inflammation (Kabbaj et al., 2012; Bouiamrine et al., 2017). Furthermore, *E. resinifera* mixed with honey has been used in traditional medicine to address a wide range of conditions, including respiratory diseases, circulatory and metabolic disorders, digestive issues, reproductive system conditions, headaches, general weakness, jaundice, angina, rheumatism, and cysts (Belhaj et al., 2020; Hmidouche et al., 2023).

Ethnomedicinal studies also report its use in oncology contexts. Samouh et al. (2019) documented the use of *E. resinifera* by patients in an oncology unit at the University Teaching Hospital Ibn Rochd in Casablanca, Morocco. In this context, natural resin preparations have been used for the treatment of various cancers, including breast, colon, lung, uterine, otorhinolaryngological (ORL) cancers, leukemia, and stomatological malignancies (Hmidouche et al., 2023).

The traditional use of *E. resinifera* varies according to the plant part and regional practices across Morocco. In several regions, it is considered a well-established remedy for cancer. Ethnobotanical studies indicate that the whole plant (fresh or dried) is widely used for its antitumoral properties (Bouiamrine et al., 2017). Additionally, decoctions prepared from resin, roots, leaves, stems, and bark are traditionally used in regions such as Casablanca for cancer treatment. In the Atlas Mountain regions of Azilal and Beni Mellal, oral administration of stems (without latex or bark) has been reported for the treatment of breast cancer and cancers of the female reproductive system (Bouiamrine et al., 2017).

Honey obtained from *E. resinifera*, is one of the most energy-dense natural foods, rich in sugars such as fructose and glucose, and containing trace amounts of essential vitamins and minerals, contributing to its recognized therapeutic properties (Abderrahim et al., 2019).

Ethnopharmacological Evidences

Traditional extraction methods, such as infusion and maceration, are widely used in herbal medicine due to their simplicity, rapid preparation, and efficiency in extracting hydrophilic bioactive compounds. These methods preferentially isolate compounds that generally lack long esterified chains and highly lipophilic aromatic diterpenes, which are often associated with irritant, pro-inflammatory, and tumor co-promoting effects upon chronic exposure (Benrahou et al., 2022). The pharmacological activities of *E. resinifera* extracts include antioxidant and antitumoral effects (Talbaoui et al., 2020; Hmidouche et al., 2023).

The immunomodulatory activity of *E. resinifera* was first demonstrated *in vitro* by Kreher et al. (1990), who reported that 12-deoxyphorbol esters isolated from latex induced lymphocyte proliferation. Subsequent *in vivo* studies evaluated both toxicological and immunological effects in young adult male mice following oral administration and gavage. These studies demonstrated that aqueous extracts of aerial parts enhanced both cellular and humoral immune responses. The high content of terpenoids, known for their immune modulatory properties, may explain the increased lymphocyte infiltration observed in tissues (Issiki et al., 2019; Hmidouche et al., 2023).

Neurological effects have also been reported, particularly for resiniferatoxin, a bioactive compound derived from *E. resinifera*. This compound exerts potent peripheral analgesic effects through activation and subsequent desensitization of TRPV1 (vanilloid receptor 1)-expressing nociceptors. It has demonstrated therapeutic potential in conditions such as detrusor hyperreflexia and overactive bladder, where modulation of the afferent branch of the voiding reflex is required (Basu, Maier, Averitt, 2016). Additionally, preclinical

studies conducted at the National Institutes of Health (NIH) Clinical Center showed that resiniferatoxin significantly reduced postoperative pain in animal models.

Further pharmacological investigations have demonstrated antitumoral activity of *E. resinifera* extracts. Talbaoui et al. (2020) fractionated latex into dichloromethane and methanol extracts and observed cytotoxic effects against kidney adenocarcinoma cell lines (BSR). Aerial parts of the plant also exhibited antitumoral properties. Moreover, Li et al. (2021) isolated five triterpenoids from latex samples collected in Xinjiang, China, and demonstrated potent anti-inflammatory activity through inhibition of nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages. Cytotoxicity assays using Cell Counting Kit-8 indicated that these compounds (euphatexols C–G) did not exhibit cytotoxic effects at tested concentrations, suggesting a favorable safety profile.

In traditional practice, *E. resinifera* is used to treat a wide range of disorders, and scientific studies corroborate several of its pharmacological properties, including antioxidant, anti-inflammatory, antitumoral, immunomodulatory, antithrombotic, and anticoagulant effects (Siritapetawee; Khunkaewla; Thumanu, 2020).

At the molecular level, certain compounds isolated from *E. resinifera* have been shown to influence key regulatory pathways. Transforming Growth Factor (TGF) is a multifunctional protein involved in cell proliferation, differentiation, migration, and immune regulation, as well as in pathological processes such as cancer, diabetes, and fibrosis. Ezzanad et al. (2021) identified two novel 12-deoxy-16-hydroxyphorbol 13,16-diesters from latex, which demonstrated the ability to stimulate TGF release via a protein kinase C (PKC)-dependent mechanism. This activity is structurally dependent on esterification at specific hydroxyl positions (C-12/C-13 or C-13/C-16), highlighting the importance of molecular configuration in determining biological activity.

Clinical Trials

The therapeutic potential of *Euphorbia resinifera*-derived preparations has been explored in both clinical and preclinical contexts. One study investigated the effects of a propolis honey–oil extract derived from *E. resinifera* on liver function in patients with chronic hepatitis C. The oil extract was prepared using olive oil and subsequently combined with honey at a concentration of 15%, using multifloral honey for non-diabetic patients and *E. resinifera* honey for diabetic patients. The formulation was administered orally three times daily, one hour before meals. The activities of serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) were monitored before, during, and after a 10-month treatment period (Mohamed, 2007 apud Hmidouche et al., 2023).

The results demonstrated a significant improvement in liver function, as evidenced by reductions in SGOT and SGPT levels across all patients during the treatment period. Additionally, patients reported a marked decrease in fatigue symptoms, including those previously unresponsive to conventional therapies. These findings support the potential therapeutic benefits of apitherapy-based formulations in the management of chronic liver diseases (Mohamed, 2007 apud Hmidouche et al., 2023).

Regarding pain management, studies have highlighted the analgesic potential of resiniferatoxin, a bioactive compound derived from *E. resinifera*. Preclinical research conducted at the National Institutes of Health (NIH) Clinical Center demonstrated that resiniferatoxin significantly reduced postoperative pain in animal models (Kuehn, 2018). Based on these findings, a phase I clinical trial was initiated at the NIH Clinical Center to evaluate the safety and efficacy of intrathecal resiniferatoxin administration. Preliminary results indicated effective pain modulation without significant disruption of nerve signaling pathways (Hmidouche et al., 2023).

Encouraged by promising *in vitro* and *in vivo* results, multiple clinical studies registered in international databases, such as ClinicalTrials.gov. have been conducted or are

ongoing to assess the safety and therapeutic potential of *E. resinifera*-derived compounds in various conditions, particularly in the context of pain management and other chronic diseases.

DISCUSSION

- Vegetal Chemistry, Phytochemistry, Toxicology from *E. resinifera*

Extensive research has been conducted on the latex of *E. resinifera*, which represents a rich source of bioactive compounds with significant therapeutic potential. Advances in extraction, synthesis, and semi-synthesis techniques continue to reveal novel molecules with promising biological activities, including anticancer and antioxidant effects (Hammad et al., 2025).

Despite these advances, the toxicological profile of *E. resinifera* remains insufficiently explored. Current evidence indicates that additional preclinical studies—particularly in vivo investigations—are essential to establish safe dosage ranges and support future clinical applications (Hammad et al., 2025).

- Pharmacological activities

The immune modulatory activity of *E. resinifera* was first investigated *in vitro* by Kreher et al. (1990). High-performance liquid chromatography (HPLC) enables the separation of components in a liquid mixture according to their affinity for stationary and mobile phases, while mass spectrometry (MS) allows the identification of molecules based on their mass-to-charge ratio (m/z). Analyses of latex-derived compounds using these techniques demonstrated that only 12-deoxyphorbol esters were capable of inducing lymphocyte proliferation *in vitro*, whereas triterpenes and ingenol esters did not exhibit significant immune modulatory activity.

Five triterpenoids isolated and identified from latex of *E. resinifera* from Xinjiang, China, were investigated by Li et al. (2021) for their anti-inflammatory properties. The

compounds, named euphatexols C–G, exhibited a moderate inhibitory effect on nitric oxide (NO) production, indicating relevant anti-inflammatory activity (Hmidouche et al., 2023).

Neurological, vascular, and infectious disorders can lead to brain damage and irreversible neuronal loss, resulting in motor dysfunction, cognitive impairment, and behavioral changes. Although the brain retains a limited capacity for neurogenesis—through neural stem cells (NSCs) located in regions such as the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus—this process is relatively restricted under normal conditions. In this context, preparations derived from the latex and aqueous extracts of *E. resinifera* may contribute to functional recovery, potentially through mechanisms associated with cellular homeostasis and detoxification to cancer patients as several official research communications, besides to neurologic manifestations from Covid19 patients (Hansel-Martins et al., 2025). Note of worthy, anticonvulsant effects have been reported for related species, such as *Euphorbia nivulia* (Rehman et al., 2019; Wasim et al., 2025).

Historically, since Szallasi (2002), the vanilloid receptor subtype 1 (VR1/TRPV1) has been recognized as a sensor for noxious stimuli located on the peripheral terminals of sensory neurons. This receptor is also expressed in various brain nuclei and non-neuronal tissues, extending its relevance beyond pain perception and increasing the potential for broader physiological effects and possible side effects following prolonged exposure to vanilloid compounds. Antinociceptive effects have also been reported for related species, such as *E. tirucalli* (Palit et al., 2018).

The vanilloid receptor subtype 1 (VR1/TRPV1) is activated by capsaicin and noxious heat, leading to the release of pro-inflammatory neuropeptides such as calcitonin gene-related peptide (CGRP), which contributes to hyperalgesia and peripheral sensitization. Potent agonists of this receptor, including resiniferatoxin and capsaicin—compounds associated with the latex of *E. resinifera* — can induce peripheral analgesia through the ablation of VR1-expressing nociceptors and subsequent receptor desensitization. These mechanisms have demonstrated therapeutic potential in conditions such as detrusor hyperreflexia and overactive bladder (Basu et al., 2016, in Gayer et al., 2025).

According to the National Institutes of Health (NIH), resiniferatoxin is structurally similar to capsaicin but is approximately 500 times more potent, with the ability to block pain-related signaling in nerve cells. Experimental studies have shown that the injection of resiniferatoxin in rats with incised paws significantly reduced pain-related behaviors compared to untreated animals (Kuehn, 2018, apud Hmidouche et al., 2023).

In 2019, the immune modulatory effects of *E. resinifera* were further investigated *in vivo* by Issiki et al. (2019) using young adult male mice. The aqueous extract of aerial parts (from Beni Mellal, Morocco) was administered at 5 g/kg body weight as a single oral dose for acute toxicity evaluation, while latex aqueous extracts were administered daily by gavage at different concentrations (0.1, 0.5, 1.0, 2.5, and 5 g/kg body weight) over 28 days for sub-acute toxicity assessment.

The results showed a significant increase in antibody titers in the group treated with a non-toxic dose (1 g/kg) compared to the control group. These findings indicate that the aqueous extract enhances both cellular and humoral immune responses, supporting its traditional medicinal use. The high content of terpenoids present in the species is likely responsible for its immune modulatory activity (Hmidouche et al., 2023).

Recent studies have shown that several phorbol derivatives—polyhydroxylated tetracyclic diterpenes present as esters in *Euphorbia* species—are capable of inducing neural progenitor cell (NPC) proliferation through activation of protein kinase C (PKC), thereby stimulating neurogenesis in regions such as the subventricular zone (SVZ) and the dentate gyrus (DG). In particular, 12-deoxyphorbol (DPB), isolated from *E. resinifera*, demonstrated a strong capacity to promote neurogenesis *in vivo* following long-term intranasal administration. In experimental models, treatment with this compound was associated with improvements in memory and learning, likely mediated by enhanced release of transforming growth factor (TGF) and increased proliferation of neural stem cells (NSCs) (Ezzanad et al., 2021 apud Hmidouche et al., 2023).

Additionally, toxicity evaluations indicated that treatment with aqueous and ethanolic extracts of *E. resinifera* over a 14-day period did not result in observable signs of intoxication

or weight loss. Based on these findings, the oral LD_{50} was estimated to be greater than 2000 mg/kg, suggesting a relatively low acute toxicity under the tested conditions (Benrahou et al., 2022).

Various *in vitro* studies have demonstrated that the scavenging activity of honey and aqueous extracts of *E. resinifera*, as well as other *Euphorbia* species, is influenced by multiple factors, including climatic conditions, botanical origin, phenolic composition, and the type of extract used. In addition, potential synergistic interactions between major and minor bioactive compounds, along with the contribution of different plant parts—such as latex—should be carefully considered.

- Ethnomedicine

In Traditional Medicine, *E. resinifera* is frequently cited in ethnobotanical studies and has been used to treat a wide range of illnesses, particularly cancer (Ernst et al., 2015; Hassan et al., 2022). *E. resinifera* is traditionally used to manage metabolic disorders, headache, weakness, jaundice, and intoxication. Moreover, clinical trials have reported low toxicity, reinforcing the safety profile suggested by traditional medicinal practices in Morocco (Bouhaya et al., 2017; 2018). Considering the biological relevance of diterpenoids, a potential phyto-adaptogenic role has been questioned (Varricchio, 2024; Gayer et al., 2025).

Within Traditional Medicine and Ethnomedicine frameworks, ethnobotanical knowledge has increasingly been supported by ethnopharmacological studies, particularly through *in vitro* models that explored mechanisms of action based on the relationship between chemical structure and biological activity (Wasim et al., 2025).

Nowadays, cancer represents a major global health challenge and imposes a significant economic burden on national healthcare systems (Voda; Bostan, 2018). According to the World Health Organization (WHO), more than 19 million new cancer cases and 10 million deaths were reported in 2020. The most frequently diagnosed cancers were breast (11.7%), lung (11.6%), colorectal (10%), and prostate (7.3%). Projections indicate that by 2040, the

number of cases may reach 24.8 million, representing a 47% increase compared to 2020 (Sung et al., 2021).

In this scenario, the development of new treatments and drugs remains a major challenge, particularly if investments in cancer care are not expanded. Limited funding can directly impact access to quality healthcare and the advancement of innovative therapies. Current strategies focus on improving therapeutic efficacy while minimizing adverse effects; however, these approaches are often complex and costly, involving advanced technologies such as novel molecular targets, nanomedicine, and bioengineering (Pucci, Martinelli, Ciofani, 2019).

The plant kingdom remains largely underexplored, although several important anticancer drugs have been derived from plant sources (Jiménez-González et al., 2023). However, there is still a lack of comprehensive research investigating the anticancer potential of different parts of *E. resinifera*, as well as the pharmacological, toxicological, and genotoxic effects of its various pharmaceutical preparations.

The recognized immune modulatory activity of Euphorbium (Kreher et al., 1990), indeed has motivated exploratory uses in recent contexts, such as attempts to prevent COVID-19 infection (El Alami; Fattah; Chait, 2020). In parallel, studies conducted with *E. tirucalli* have investigated molecular pathways involving p53 and TGF-β (previously made by Chen et al., 2015; Archanjo et al., 2016), highlighting the importance of regulatory balance between pathways such as p53 and NF-κB, whose dysregulation may contribute to triggering neoplastic processes (Milani et al., 2022).

These findings have significantly increased scientific interest in understanding the mechanisms of action of compounds derived from *Euphorbia* species, rigorously studied (Betancur-Galvis et al., 2003), particularly in relation to their potential therapeutic applications and associated risks (Wasim et al., 2025; Kgosiemang et al., 2025).

In parallel, our group has developed comprehensive studies in Environmental Immunology (Ximenes et al., 2023; Rebelo et al., 2025, 2025a), focusing on the mitigation of cellular oxidative stress. This approach is particularly relevant in the current global context,

where oxidative imbalance has increased significantly, especially in populations previously exposed to SARS-CoV-2 and living with its long-term sequelae (Hansel-Martins et al., 2025).

The variation in terpenoid profiles across different phenological stages represents a key parameter for investigation. So, in *E. resinifera*, such variation may influence latex composition, polyphenol content, and the overall profile of secondary metabolites throughout plant development. Furthermore, *E. resinifera* honey studies have been suggested to exhibit phyto-adaptogenic action and cellular scavenging properties, indicating its great potential role as a functional food. These characteristics align with ongoing research in innate environmental immunology and support the evaluation of Euphorbia honey as a possible candidate for translational and clinical research (Hansel-Martins et al., 2025; Wasim et al., 2025).

Despite the growing number of pharmacological studies on *E. resinifera*, there is still a lack of toxicological data derived from different geographical regions and edaphoclimatic conditions (Varricchio et al., 2024). The empirical use is a serious limitation and highlights the need for expanded toxicological investigations to ensure safe and standardized use (Gayer et al., 2025).

Finally, from a pharmacokinetic perspective, studies focusing on cytochrome P450 interactions are still scarce. This represents a major bottleneck in the transition from basic research on *Euphorbia* species to clinical application. Therefore, comprehensive investigations into pharmacokinetics and pharmacodynamics are essential to guide therapeutic targeting and to ensure drug stability and safety, particularly in the context of complementary cancer therapies—an area of increasing global demand given the rising burden of the disease and the need for effective palliative care (NIH, 2018; Barreto et al., 2026).

Propolis and *Euphorbia* Honey

Nearly 1000 years ago, a famous Iranian scholar and physician recommended honey as one of the best treatments for curing tuberculosis, a fact later confirmed by clinical trials (Efremenko et al., 2012).

Honey is a natural sweetener composed of various macro and microelements, such as carbohydrates (glucose and fructose), whose main constituents represent approximately 95% of its dry weight, along with other minor constituents such as vitamins, enzymes, organic acids and amino acids, proteins, volatile organic compounds (VOCs), various polyphenols, minerals, and pollen grains (Alvarez-Suarez, 2017).

Honey is bactericidal, anti-septic, anti-rheumatism, vasodilator, diurethic, digestive, tonic, hiperglicemic, sedative, vermifugous and acts as an adjuvant in respiratory, cardiac, visual and throat affections. Resin honey, propolis, is collected in several plant parts. It is a natural sterilizer that protects a hive of foreign bodies and epidemics. In the past, propolis was frequently used in mummification process in Egypt. For all motives, honey and propolis are also good health environmental indicators of sanity (Varricchio, 2024; Wendling da Silva et al., 2025).

It is considered a functional food or a nutraceutical. It is frequently used to treat respiratory diseases such as asthma and bronchitis, pyelonephritis with cysts, and cancer. Many treatments in traditional Moroccan medicine employ honey, either pure or in combination with powdered honey (Moujannie et al. 2017). It is worth noting that Euphorbia honey is among the most expensive types of honey and is considered very valuable by Moroccan, Lebanese, and Turkish consumers (Bettar et al. 2019; Bouhlali et al. 2019; Kivrak; Kivrak 2017). In fact, it is considered a medicine, especially in cases of asthma, cysts, and cancer, justifying its high cost in these regions (El Orfi et al., 2022).

The physicochemical parameters of honey, its chemical constituents and, consequently, its therapeutic merits vary according to its geographical and botanical sources, harvesting and handling processes and storage period (Alvarez-Suarez, 2017). Regarding the botanical classification of the floral species from which bees collect nectar, there are two

widely used types of honey: monofloral (unifloral) and polyfloral (multifloral) (Sahri et al., 2023).

Euphorbia honey, a monofloral food also known as "Daghmous honey" or "Zakoum honey," depending on the species, is a common product of the Mediterranean region (Imtara et al. 2019). Morocco is the largest producer of Euphorbia honey due to apicultural interest and the various Euphorbiaceae plants (*Euphorbia* L.) endemic to the country (Bettar et al. 2019; Bouhlali et al. 2019; Lyoussi et al. 2022).

Euphorbia honey comes from succulent plants of the Euphorbiaceae family. Morocco produces three types of honey: *E. resinifera* (Middle Atlas region, with isolated populations in the High Atlas and Anti-Atlas mountains); and *Euphorbia officinarum subsp. equino*; *Euphorbia officinarum subsp. officinarum*; and *Euphorbia Regis-jubae* (southwest Morocco; Boutoub et al., 2021).

The best-known species used in beekeeping include: *E. resinifera*, *E. officinarum, E. echinus, and E. bupleurifolia.* The reviewed studies were conducted in North African countries such as Algeria and Morocco and reported a significant underrepresentation of *Euphorbia* honey, with a minimum of 25% of pollen derived from other Euphorbia spp. species (after excluding pollen grains from non-nectar and anemophilous plants). The main companion species that typically coexist with *E. resinifera* include *Ceratonia siliqua*, *Echium plantagineum*, Olea sp., *Plantago coronapus*, and Quercus (Imtara et al., 2019; Terrab et al., 2002; 2003, 2014; 2022).

Regarding phytochemicals, this genus is reported to contain phenolic acids, flavonoids, glycerols, steroids, phytosterols, glycosides, cerebrosides, tannins, alkaloids, saponins, anthraquinones, and terpenes, including diterpenes and triterpenes, along with bioactive proteins, including proteases, oxidases, lectins, and chitinases (Carlini; Grossi-de-Sá, 2002; Elgamal et al. 2021; Sytwala et al. 2015; Zhao et al. 2022). Due to these phytoconstituents, their species provide a diverse range of medicinal properties, such as antibacterial, antifungal, antiviral, anti-inflammatory, cytotoxic, anxiolytic, anti-aging, antidepressant and antidiabetic activities (Badaoui et al., 2022; Zhao et al., 2022).

Regarding amino acids, proline was the most investigated in Euphorbia honey, with values ranging from 441.67 to 1169.45 mg/kg. The detection of proline in honey at a concentration of 180 mg/kg or higher is generally considered a reliable indicator of high quality and purity (Bouhlali et al., 2019). However, no studies have been conducted to evaluate the content of glutamic acid, alanine, tyrosine, leucine, phenylalanine, and other amino acids in Euphorbia (Sahri et al., 2023).

The main phenolic components found in Euphorbia honey are phenolic acids and flavonoids. Phenolic acids comprise a group of compounds that includes derivatives of cinnamic and benzoic acids. Benzoic acid derivatives include protocatechuic acid, 4-hydroxybenzoic acid, gallic acid, vanillic acid, and syringic acid, while cinnamic acid derivatives include caffeic acid, coumaric acid, O-coumaric acid, and ferulic acid (Boutoub et al. 2021a; Hernanz et al. 2022; Imtara et al., 2019; Kivrak; Kivrak, 2017).

Flavonoids in Euphorbia honey have been elucidated as chrysin, apigenin, luteolin, hesperetin, kaempferol, quercetin, rutin, naringenin, and epicatechin (Boutoub et al., 2021b; Hernanz et al., 2022; Imtara et al., 2019; Kivrak, 2017). However, further investigation is needed to quantify other flavonoids, such as pinocembrin (5,7-dihydroxyflavone), an organic compound found in bee products, mainly propolis and honey, which possesses numerous pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, neuroprotective, anticancer, and cardioprotective activities (Elbatreek et al., 2023).

Honey and its constituents, such as chrysin, pinocembrin, and proline, have been used as nutritional supplements, and their bioactive properties have positioned them as vital components of various nutraceuticals, phytochemicals and phytopharmaceuticals. Furthermore, their potential to act synergistically with conventional medications has led to their use as adjuvants to enhance the therapeutic or cytotoxic effects of these drugs (Martinez-Armenta et al., 2021).

Oxidative stress, inflammation, and apoptosis are fundamental physiological processes that play essential roles in the pathogenesis of various diseases. The use of phenolic compounds from honey as a treatment for disorders associated with these processes has

demonstrated a considerable capacity to modify clinical outcomes by modulating these underlying mechanisms and their associated signaling pathways (Rahman et al., 2021).

Similarly, proline and proline-rich polypeptides (composed of fifteen amino acid residues) have been shown to possess immune regulatory, hematopoietic, antineurodegenerative, antitumor, and antimicrobial properties. The cytostatic and cytotoxic impact of proline-rich polypeptides has been demonstrated in triple-negative breast carcinoma cell lines MDA-MB-231 and in human chondrosarcoma JJ012 (Rahman et al., 2021).

Although numerous studies have investigated the cytotoxic and cytostatic properties of various types of monofloral honey (Abrahamyan et al. 2020; Bose et al. 2022; Moreira et al. 2020), research of this type has been scarce and infrequent regarding the cytotoxic and cytostatic effects of *Euphorbia* honey. Imtara et al. (2019) studied the cytotoxic and cytostatic effects of twelve honey samples collected from various locations in Palestine and Morocco, including *Euphorbia* honey, which exhibited cytotoxic and cytostatic effects on the MCF-7 breast cancer cell line and on the HCT-116 human colorectal carcinoma cell line, at a concentration of 2000 µg/ml, and this effect was mainly attributed to the polyphenol and flavonoid content of the honey.

Furthermore, it is known that wounds can be acute or chronic. Coagulation, inflammation, proliferation, and remodeling are the four stages of the ordered and complex process that is wound healing (Bouzroud et al., 2023). Agents with antioxidant, anti-inflammatory, and antimicrobial properties are promising candidates for use in the wound healing process (Mahdi et al., 2023). One such substance is honey, which can be used to heal a variety of wounds due to its beneficial properties, particularly its antibacterial activity (Bhushanam et al., 2023).

Euphorbia honey plays a crucial role in wound healing processes due to its antibacterial, anti-inflammatory, and antioxidant properties, immune system-boosting effects, debriding action, and stimulating involvement in wound regeneration. Previous studies have shown that Euphorbia honey improves the healing of acute wounds, an effect potentiated by the addition of garlic (Ait Abderrahi et al., 2019). Euphorbia honey improved the healing of

enucleation wounds in cattle through its anti-inflammatory, analgesic, and antibacterial activities (Khiati et al., 2013).

Highly nutritious, *Euphorbia* honey also possesses antioxidant properties (Aazza et al. 2014), antimicrobial properties (Ait Abderrahim et al., 2019; Benjamaa et al. 2020; Latifa 2020), anti-inflammatory, healing, antimutagenic and anticarcinogenic effects (Badolato et al. 2017) along with a potential enzyme inhibitory effect (Boutoub et al. 2021, 2021a).

Although honey allergies are rare, caution is important to avoid adverse reactions. Furthermore, it is important to emphasize that the composition of honey can be affected by adulteration, a serious problem that has become a concern due to the increasing complexity of adulteration techniques, which, in some cases, are difficult to detect and can have adverse effects on the human body, especially on the renal system (Sahri et al., 2023).

Finally, propolis honey–oil extract derived from *E. resinifera*, used in Traditional Medicine in Morocco, seems to have a very promissor effect in cancer patients and Tuberculosis, besides chronic illnesses with cutaneous lesions and wounds (should be tested in Cutaneous Leishmaniasis and Hanseniasis), besides illnesses from viruses as Covid19 (Hansel-Martins et al., 2025). So, it is of great interess in basic research to perform pre-clinical studies, but also to act as a sanity environmental bioindicator (Wendling da Silva et al., 2025), while it can also be used to protect external area of a hive is *situ* an apiary (Sandra Ávila Gaspar, oral communication 2026, Apr 30).

Limits of Study

Although studies on *Euphorbia resinifera* have been conducted in different regions, a substantial portion of the available data originates from a limited geographical context, particularly Morocco. This geographical concentration may introduce bias, as environmental, edaphoclimatic, and genetic variations can significantly influence phytochemical composition and biological activity. Consequently, the extrapolation of these findings to other regions should be approached with caution.

In addition, most available studies are based on *in vitro* and *in vivo* experimental models, with a limited number of well-controlled clinical investigations. Variability in extraction methods, plant parts used, and experimental conditions further complicates the comparison and reproducibility of results. Moreover, comprehensive toxicological, pharmacokinetic, and pharmacodynamic data—especially across medical demography (observing different populations) besides long-term exposures—remain scarce.

Contribution

This review highlights the significant pharmacological potential of *Euphorbia resinifera*, particularly due to its diverse bioactive compounds, including terpenoids and phenolic constituents. The available evidence suggests that these compounds may exert relevant biological activities, such as antioxidant, anti-inflammatory, and immunomodulatory effects, supporting their potential application in chemopreventive strategies and as complementary approaches alongside conventional therapies, including chemotherapy and radiotherapy. However, such applications still require robust clinical validation.

The traditional use of *E. resinifera* in association with conventional medicine is partially supported by experimental and emerging clinical evidence reported in the literature that bring a great potential to pre-clinical research as Tuberculosis (Safwat et al., 2018) and as Neglected Diseases (Cazumbá et al., 2025). Meanwhile, its pharmaceutical prepare as *Euphorbium* with presence of the ingenol, a terpene with propriety of induce apoptosis (Girin et al., 1993) may assure it may be applied in translational medicine to oncologic patients (Zissu, 2011; Paiva et al., 2011), specially with untreatable and excruciating pain (Gayer et al., 2025; Wasim et al., 2025a).

In particular, *E. resinifera* presents promising biotechnological potential for investigation within the tumor microenvironment. Preliminary evidence suggests that its bioactive compounds may influence lysosomal activity and cellular processes relevant to cancer biology (Hmidouche et al., 2023). Therefore, both species represent valuable targets

for further basic and translational research, specially as ointments to torpid cutaneous lesions (Thiery et al., 2009; Palit et al., 2018; Abderrahim et al., 2019; Newman; Cragg, 2020; Jiménez-González et al., 2023; Kgosiemang et al., 2025).

Specially, Euphorbia honey as a functional food to scavenger and to immune modulator activities (Boutoub et al., 2021, 2021a; Hmidouche et al., 2023).

CONCLUSION

Overall, the evidence gathered in this review is consistent across ethnomedicinal knowledge, phytochemical characterization, pharmacological investigations, and the limited clinical studies available worldwide.

Despite these advances, it remains essential to rigorously demonstrate safety, efficacy, and detailed pharmacological mechanisms of action, as highlighted. Future studies should adopt robust and standardized methodologies, particularly in anticancer research across multiple tumor types, to better define the therapeutic potential of *E. resinifera*. In addition, its possible effects on chronic and neglected diseases—including those with oncogenic potential —deserve further investigation.

Natural products remain a rich and largely underexplored source of bioactive molecules with therapeutic potential. This review aimed to synthesize the current state of the art on *E. resinifera* (latex and honey) to encourage further multi and interdisciplinary research efforts to Cancer as it is frequently used for treatment.

But here, propolis and *Euphorbia* honey were presented focusing specially to its possibility of use in Tuberculosis, an infectious disease not controlled around the world; besides, maybe, the use as an adjuvant in Hanseniasis, a millennial illness still out of control in the world, even with poliquimiotherapy, so, pointing to necessity of reinforcing host immunity.

Finally, propolis and *Euphorbia* honey are effective, cheap and administered by oral way as a functional food. Indeed, this investigation seems to be very promissor to

contemporary serious global problems as war refugees with lasting disabilities, besides people with serious chronic illnesses (some of them neglected), in situations of severe food insecurity.

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