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Review

Euphorbia neriifolia (Indian *Spurge* Tree): A Plant of Multiple Biological and Pharmacological Activities

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Abstract: Although India has a well-established and growing economy surrounding synthetic drug chemistry with an antibiotic base, a large part of the population, especially in forested villages and tribal belts, is relying solely on plant-derived drugs. This is due to a lower number of side effects, low chances of resistance development against pathogenic microorganisms, as well as the diversity and affordability of such drugs. In the Indian subcontinents, *Euphorbia neriifolia* Linn. (EN) is one of the valuable plants from the big family of *Euphorbiaceae*, which is usually found in rocky and hilly areas. *E. neriifolia* was found to be useful in curing tumors, abdominal swelling, bronchial infection, hydrophobia, earache, cough and cold, asthma, leprosy, gonorrhea, spleen enlargement, leucoderma, snake bites, scorpion stings, and causing appetite improvement, etc. Different in vitro and in vivo experimental studies were performed to determine the antioxidant, anti-diabetic, immunomodulatory, anti-inflammatory, anti-arthritic, wound healing, anti-atherosclerosis, radioprotective, anti-anxiety, anti-convulsant, anti-psychotic, anti-thrombotic, dermal irritation, hemolytic, analgesic, anti-fertility, diuretic, anti-microbial, anti-diarrheal, and anti-carcinogenic activities of the various parts of EN. Several bioactive compounds, such as euphol, nerifoliol, taraxerol, euphonerins A–G, lectin, etc., were isolated from *E. neriifolia* and need to be investigated further for various biological activities (cardiovascular and neuronal diseases). In the pharmaceutical sector, *E. neriifolia* was selected for the development of new drugs due to its broad pharmacological activities. Therefore, in the present review, distribution, classification, morphological and microscopical description, phytochemical investigation, pharmacological activities, medicinal uses, harmful effects, and their treatment were evaluated, especially against different lifestyle-related diseases.

Keywords: bioactive compounds; *Euphorbia neriifolia*; lifestyle-related diseases; morphological description; pharmacological activities

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1. Introduction

Since ancient times, people have searched for drugs in nature to cure their illnesses. There was no information concerning the cause of the disease or the medicinal plants, such as how to use them for treatment; everything was based on experience alone [1]. Many plants species from different parts of the world have been proposed for medicinal use as they are composed of various types of chemical compounds, such as secondary metabolites with different biochemical activities [2]. According to the World Health Organization (WHO) [3], almost 80% of the global population is still dependent upon the traditional system (Ayurvedic, Sidha, Tibetan, Unani, Rigpa, Sowa, Folk, Homeopathic, and Chinese) of medicines for the betterment and well-being of their lives. Most of the treatments include active components and extracts from the medicinal plants [4]. The difficulty in the formation of chemical-based drugs, along with increasing costs and health-related side

effects, has led researchers to focus on medicinal plants [5]. The demand for naturally derived drugs has gained significant attention in both developed and developing countries because of their accessibility, preventive nature, diversity, affordability, and the safety of natural bioactive agents present in the plants [6].

Traditional medicinal systems have created a base of early medicines with chemical, pharmacological, and subsequent studies. Some of the well-known examples to date include salicin derived from the bark of *Salix alba* L., morphine isolated from *Papaver somniferum*, quinine isolated from *Cinchona succirubra* bark, pilocarpine derived from *Pilocarpus jaborandi,* etc., for the treatment of inflammation, congestive heart failure, fever, and chronic and acute glaucoma [7]. To hold a better position in both traditional and modern systems of medicine across the globe, the *Euphorbia neriifolia* Linn. plant needs to be characterized and its use standardized in terms of diversity and pharmacological activities [8]. The family *Euphorbiaceae* consists of approximately 800 species, 317 genera, and 49 tribes. A large number of species from the genus *Euphorbia* are under the snuk name and its synonym. *Euphorbia neriifolia* is a deciduous, large succulent medicinal plant with stipular thorns that is usually found throughout the Orissa and Deccan Peninsula in India [9]. This plant is widely known for its therapeutic activities, such as anti-viral, anti-convulsant, radioprotective, anti-arthritic, anti-asthmatic, anti-fertility, anti-diarrheal, and anti-ulcer activities [10]. Different types of diterpenoids with variable skeleton, such as eurifoloids A–R, eupnerias G–I, and eupnerias J–M, were isolated from *E. neriifolia* plants. Anti-HIV and cytotoxic activity against HepG2/Adr cell lines are the related pharmacological activities that were reported for these diterpenoids [11]. Some triterpenoidal compounds, such as neritroterpenols A–B, C, and D–G; turucallane triterpenes; and euphane from the stem of *E. neriifolia* are reported to have anti-proliferative and anti-inflammatory activities, respectively [12]. The research into natural compounds is relevant, and there are compounds used in clinical practice from natural sources. Furthermore, since plants have been used in treating various pathologies since ancient times, it is essential to validate these traditional applications and simultaneously study new compounds with relevant biological potential. Thus, the present review on the *E. neriifolia* plant includes all the information from 1963–2022 related to distribution, botany, phytochemistry, and biological and pharmacological activities.

2. Etymology, Distribution, and Origin

The "*Euphorbia*" genus was named in honor of the physician (Euphorbus) of King Juba II (25 B.C–18 B.C.). King Juba II was keenly interested in the flora of Mauritania, and he found a latex producing plant in the hilly and rocky area in his domain. According to some reports, the *E. neriifolia* was named after "Linnaeus" [13] and the meaning of *neriifolia* is "leaves like an oleander" [14]. Approximately 195 species of *Euphorbia* are found in India, and they are divided into two types: geophytic and dendroid species [15]. Other *Euphorbia* species (*Euphorbia royleana*, *Euphorbia nivulia*, *Euphorbia acaulis, Euphorbia nana, Euphorbia humilis, Euphorbia sahyadrica, Euphorbia venkatarajui, Euphorbia panchganiensis, Euphorbia khandallensis, Euphorbia trigona, Euphorbia pycnostegia, Euphorbia royleana, Euphorbia antiquorum, Euphorbia rosea*, *Euphorbia rothiana*, *Euphorbia milii*, *Euphorbia santapaui*, *Euphorbia thymifolia*, *Euphorbia tithymaloides*, *Euphorbia tirucalli*, *Euphorbia cyathophora*, *Euphorbia lactea*, *Euphorbia thomsoniana*, *Euphorbia heterophylla*, *Euphorbia helioscopis*, *Euphorbia cyathophora*, *Euphorbia pulcherrima*, *Euphorbia leucocephala*, *Euphorbia inaequilatera*, *Euphorbia indica*, *Euphorbia nodosa*, *Euphorbia prostrata*, *Euphorbia cristata*, *Euphorbia pallens*, *Euphorbia tortilis*, *Euphorbia thomsoniana*, *Euphorbia concanensis*, *Euphorbia terracina*, *Euphorbia dracunculoides*, *Euphorbia acaulis*, *Euphorbia katrajensis*, *Euphorbia acaulis*, *Euphorbia graminea*, *Euphorbia humifusa*, *Euphorbia heyneana*, *Euphorbia eriophora*, *Euphorbia wallichii*, *Euphorbia fusiformis*, *Euphorbia erythroclade*, *Euphorbia deccanensis*, *Euphorbia katraiensis*, *Euphorbia elegans*, *Euphorbia cognate*, *Euphorbia decaryi*, *Euphorbia hypericifolia*, *Euphorbia hispida*, *Euphorbia tibetica*, *Euphorbia helioscopis*, and *E. neriifolia*, etc.) are commonly found in India [16]. *E. neriifolia* is usually found in rocky ground and the rock crevices in hills. The plants of *E. neriifolia* are cultivated for fencing

purposes in Sri Lanka, Ceylon, Burma, Baluchistan, and Malaysian island and for hedges in Bengal and other nearby villages [17].

2.1. Scientific Classification of *Euphorbia neriifolia*

The scientific classification of *E. neriifolia* is listed in Table 1 [18].

Table 1. Classification of *Euphorbia neriifolia* Linn.

***Euphorbia neriifolia* Classification**	
Kingdom	Plantae—Plants
Subkingdom	*Tracheobionta*—Vascular plants
Super-division	*Spermatophyta*—Seed plants
Division	*Magnoliophyta*—Flowering plants
Class	*Magnoliopsida*—Dicotyledons
Subclass	*Rosidae*
Order	*Malpighiales*
Sub-order	*Euphorbiales*
Family	*Euphorbiaceae*
Sub-Family	*Euphorbioideae*
Tribe	*Euphorbieae*
Sub-Tribe	*Euphorbiinae*
Genus	*Euphorbia*
Species	*neriifolia* Linn.

2.2. Synonyms

Euphorbia neriifolia Linn is morphologically similar with a number of other species from genus *Euphorbia,* such as *Euphorbia ligularia* Roxb., *Euphorbia antiquorum* Linn. (Tridhara sehunda), *Euphorbia nivulia* Buch. (Ham), *Euphorbia royleana* Boiss. (Thuhara), *Euphorbia tirucalli* Linn. (Kanda snuhi), *Euphorbia caducifolia* Haines. and *Euphorbia trigona* Haw (Tridhana sehunda bheda) [19].

2.3. Classical Categorization

EN is classically categorized into the following: (i) Dhanvantari Nighantu (Guduchyadi varga), (ii) Kaiyyadeva Nighantu (Oushadhi varga), (iii) Shodala Nighantu (Guduchyadi varga), (iv) Bhavaprakasha (Guduchyadi varga), (v) Raja Nighantu (Shalmalyadi varga) [18,20–25].

2.4. Vernacular Names

Euphorbia neriifolia is known with variable names in different regions (Table 2) and languages, which are as follows [18,20–25].

Euphorbia neriifolia is known by different names in various languages based on its properties and functions as listed in Table 2. For example: in Sanskrit, the meaning of its name is as follows: (i) Sudha—has white colored latex; (ii) Samanth dugdha—has milk all over the body; (iii) Vajradruma, Vajrakantaka, Kulisha druma, Vajravruksha, Vajratunda, Vajri—it has strong action similar to diamond, branches are diamond shaped in cross section; (iv) Nistrisha patra—the structure is sharp, similar to a sword; (v) Mahavriksha—the shrub grows to a good height; (vi) Vatari—balances vata dosha; (vii) Ksheerakanda, Bahushrava—yields profuse latex; (viii) Bahushakha—multiple branches, (ix) Dabdavruksha—branches are as log of woods [25].

Table 2. Vernacular names of *Euphorbia neriifolia* in different regions.

Regions	Vernacular Names
Arabic	Dihu Minguta, Rumid, Lebbain, Azfurzukkum, Jauarulkalb
Bengal	Mansasij, Hijdaont, Hijdaona, Hildaona, Patashij, Tiktasij, Shij
Bombay	Nivadunga, Thohur
Burmese	Thassaung, Shasaung, Zizaung, Thazavn-mina, Shazawnminna
Deccan	Kuttekijibhkasend, Kuttekijibhkapatta
Different regions	Variable names
English	Hedge Euphorbia, Oleander Spurge, Milk hedge, Dog's tongue, and Indian Spurge Tree
Goa	Nevulkanta
Gujarati	Thor, Tuaria, Kantaluthohar, Kantalo
Hindi	Thuhar, Sij, Sehund, Patton-ki-send, Danda-thuar, Danda-thor, Gangi-chhu
Ilocano	Carambuaya
Indochinese	Xuong rong, Xuong rong ta
Kannada	Muru Kanina Kalli, Yelekalli, Aelaegalli, Elekalli, Gootagalli, Irekalli, Yellegulla
Kashmiri	Kath
Konkani	Nivalkantem, Nivelkanti
Maharashtra	Vayinivadunga
Malaya	Sesudu
Malayalam	Kalli, Elakkalli, Ilakkalli
Marathi	Mingut, Newarang, Neya-dungra
Oriya	Siju, Kantalothor
Pampangan	Bait, Sosoro
Philippines	Lengua de perro, Carambuaya, Karimbuaya, Sobog-sobog, Sobo-soro
Punjabi	Gangichu, Thor
Rajputana	Thor, Patton ki send
Sanskrit	Snuhi, Sudha, Vijri, Snuk, Svarasana, Patrosnuhi, Sudhi, Nistrinsapatra, Pratrasnuk, Puttakarie, Sakhakanda, Samantadugdhaka, Seej, Vajra, Vajravrksa, Vujri, Ilai-kalli, Aranciruku, Caciyami, Camattuttaccam, Catakkai, Cinittam, Cunkatam, Katutittacam, Kunakki, Manar, Manca
Sinhalese	Paluk, Patuk
Tamil	Ilaikkalli, Kalli, Manjevi, Nadangi, Naynakki, Perumbukalli, Mucarcevi, Mutakapani, Mayurpelakkalli, Nakanay, Nalainkalli, Natanki, Nattanki, Naynakku, Payaca, Mulaittaci, Picakavayakkalli, Pilavaillolli, Punakam, Sadurakalli, Talaikkalli, Tapilika, Terravacceti, Ulokapantani, Vattampam, Vaccirakanta, Vannikaram
Telugu	Akujemudu, Kadajemudu
Thailand	Som chao
Tibetan	Snu-ha
Urdu	Zaqqum, Sendh, Send, Thuhar

2.5. Unani Classical Literature Description

Thuhar containing milky latex is considered a type of herbal drug. In the Unani classical literature, there are various varieties of Thuhar, such as (i) Chaudhara thuhar with quadrangular stem and leaves; (ii) Tadhara thuhar with triangular stem and leaves; (iii) Danda thuhar with round leaves and stem [26].

2.6. Temperament

According to Ayurvedic physicians, the nature of *E. neriifolia* plant is dry and hot. Some classify it as dry and hot in the second degree, while others consider it in the third degree. The latex of *E. neriifolia* is reported to be dry and hot in the fourth degree [27].

3. Cultivation Needs

Euphorbia neriifolia plants need proper sunlight for their better growth but they can also adapt to grow in the shade as well. They are also found to grow in dry places over the rocky areas in the drained soil of the different villages in India. They quickly grow into large trees without the requirement of any maintenance within a 3–5 year time period. Watering them on a regular basis is required during the growth season (March to September), but collection of water near the root area should not be allowed and they should be kept completely dry in the winter season [28]

Seasonal Collection of Crude Drugs

According to Charak samhita, different seasons for the collection of different parts of *E. neriifolia* are mentioned in Table 3. As per Sushrut Samhita, the most preferable time of collection for *E. neriifolia* fruit is the summer season (Grishmaritu), for latex is the early winter (Hemantritu), for the bark is the autumn season (Sharadritu), for the leaves is the rainy season (Varsharitu), and for the roots is before the rainy season (Pravrutaritu) [29].

Table 3. Season of collection for different parts of *Euphorbia neriifolia*.

Different Parts of *Euphorbia neriifolia*	**Season of Collection**	**References**
Leaf and branches	Spring (Vasantritu) and rainy season (Varsharitu)	[29]
Root	Late winter (Shishirritu) and summer (Grishmaritu)	
Latex, rhizome, and bark	Autumn (Sharadritu), heartwood (Sarabhaga), and early winter (Hemantritu)	
Fruit and flower	Ritu	
Plants with hot potency	Summer (Grishmaritu)	
Plants with cold potency	Late winter (Shishirritu)	

4. Morphological Description

The morphological description of *E. neriifolia* is discussed below and represented in Figure 1.

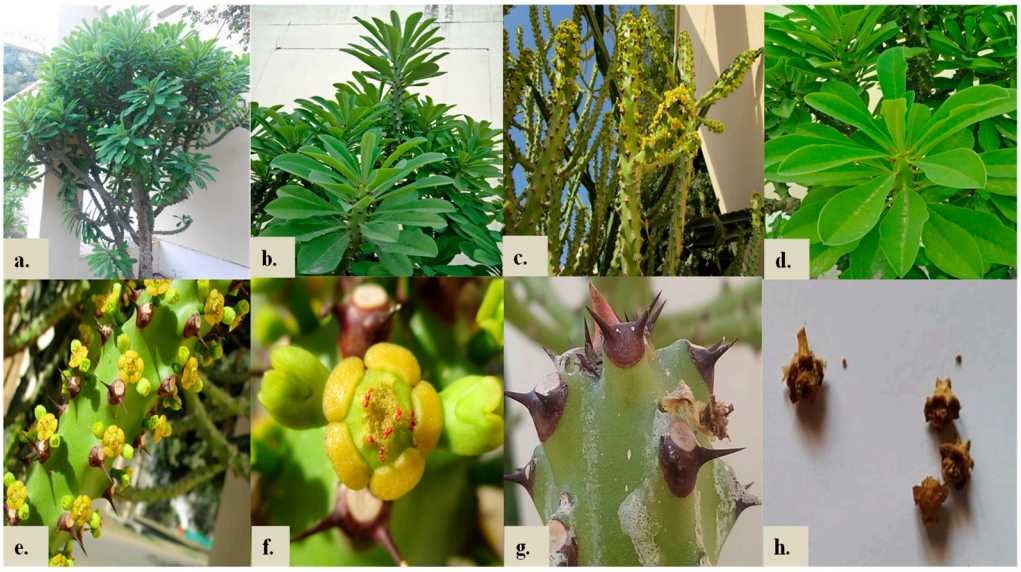


Figure 1. Macroscopic view of *Euphorbia neriifolia* and their aerial parts: (**a**) *E. neriifolia* plant, (**b**) fresh leaves, (**c**) plant with inflorescence and without leaves, (**d**) branch showing the arrangement of leaves, (**e**) young inflorescence-cyathium type, (**f**) flower with stigma, (**g**) stipular thorns, (**h**) seed of *E. neriifolia*.

4.1. Whole Plant

Euphorbia neriifolia is a xerophytic shrub or tree of 20 ft that is succulent, branched, and glabrous when erect. Saccular straight branches with strong stipular spines in pairs on tubercles allow these tubercles to be more or less confluent in five slightly or vertical spinal ribs or lines. These branches are 5-gonous in section. A bundle of thick succulent leaves occurs at the terminal position on the branchlets. The *E. neriifolia* bark is reticulated in nature and covers the complete trunk of a 7.5 m tree [28,30].

4.2. Stem

The stem of *E. neriifolia* is cylindrical in shape and of a green color. It consists of a white-colored reticulate mass in the center with a hollow space, stipulated and sharp thorns, and a spiral ridge. The taste of *E. neriifolia* stem is acrid and astringent. The dried stem can be broken easily, which results in the exposure of hollow pith attached to white-colored parenchymatous papery scales [31,32]. The organization of the *E. neriifolia* shoot apex was reported by Shah and Jain [33], whereas Arumugasamy et al. [34] analyzed the secretion and ultrastructure of *E. neriifolia* from cyathial nectarines.

4.3. Leaves

The leaves of *E. neriifolia* are pungent, a bitter laxative, and carminative. They narrow into a short petiole, have a lathery texture, and are 6–12 inches long, terminal in position, and succulent and deciduous in nature. *Euphorbia neriifolia* usually remains leafless for the whole year but it bears leaves from monsoon season to the month of November. The average thickness, breadth, and length of *E. neriifolia* is 1.3 $\pm$ 0.2 mm, 8 $\pm$ 2 cm, and 8 $-$ 14 $\pm$ 2 cm with an acute and pointed tip. The peri-clinical divisions at the fourth or third peripheral meristem layer initiate the formation of the leaf [9,23].

4.4. Stippular Thorns

The thorns are persistent, arising from ribs, sharp, blackish to brown in color, short in size, and approximately 4–12 mm long. These are distant from the low conical and spiral-arranged tubercles 2–3 cm apart and 2–5 mm in height [28].

4.5. Inflorescence

Flowers of *E. neriifolia* are arranged in a cyanthium-type manner that involves one female and many males in a group on the same bunch. The female flowers develop into fruits and have a tri-chambered ovary, whereas male flowers are bract, linear, and more in number. The development of female into flower is very rare and they have an ovum in each chamber [28].

4.6. Involucers

EN involucres are yellowish 3-nate with centrally sessile, fimbriate, most abundant bracteoles; transverse oblong glands; and are cordate, erect, roundish, and large lobed, whereas the lateral cyme is pedicelled thick and short in size. There are three capitate and style stigmas that often bifurcate into two. Capsules are deeply three-lobed, and approximately 0.5 inches wide, but sometimes seeds and capsules are not seen [23] (Figure 1).

4.7. Fruits

The fruits of *E. neriifolia* are tricoccaus, i.e., similar in appearance to a capsule (10–12 mm in diameter) with three chambers, and greenish yellow in color but with three radiating type slender follicles [23,28].

4.8. Seeds

Seeds are similar in size to a mustard grain (2.00 $\pm$ 2.5 mm in diameter) and grayish-brown in color. They are flat and contain soft hairs [32].

4.9. Latex

Fresh *E. neriifolia* latex contains 16.23 to 24.50% triterpenes and diterpenes, 18.32% total resinous matter, and 10.95% solid matter. Approximately 10% of angiosperms and flowering plants contain milky, sap-like latex. The sap of *E. neriifolia* latex is a mixture of glycosides, ricin-type protein that is toxic in nature, triterpenes, alkaloid, and polycyclic diterpenes. Defense-type substances are also reported at 50–1000% in the case of *E. neriifolia* latex [30]. The latex of *E. neriifolia* is a white-colored, sap-like liquid. This sticky and lathery textured latex is found inside the vessels or cells and commonly released after any tissue injury to maintain the laticiferous system [29].

5. Microscopic Description

5.1. Leaf

The transverse section of *E. neriifolia* leaf has shown thick, single-layered tubular to rectangular shaped adaxial epidermal cells. The abaxial epidermis is single to double layered and contains rectangular to circular shaped epidermal cells. The *E. neriifolia* leaf is reported to have anomocytic stomata surrounded with guard cells and 2–3 subsidiary cells. The adaxial side of the *E. neriifolia* leaf contains a greater number of stomata than the abaxial side. The bicellular head glandular trichomes and blunted tip trichomes, which are five celled unicerate, are reported in certain regions of the epidermis [23]. The differentiation of mesophyll tissue was performed in two to three layers of radially elongated palisade cells in the adaxial zone and broader spongy mesophyll cells that further divided into dorsiventral lamina. The spongy mesophyll contains partition filaments and air-chambers that are generated by interconnected and lobed 6–9 layered spongy parenchymatous cells. The region of the midrib is semi-circular on the adaxial side and slightly risen on the abaxial side. The midrib is composed of the epidermis, collenchyma, and spongy parenchyma cells [28]. The vascular bundles are more prominent at the ventral side and contain non-lignified phloem and lignified xylem. Transfusion tissues were observed in the parenchymatous cell region of the leaf after it was stained with acid. Thick, octahedral, loosely arranged, rosette-shaped calcium oxalate crystals were observed between the spongy cells. The presence of starch granules was observed after staining the spongy parenchymatous cells with potassium iodide. The surface of the leaf also showed the presence of vein, vein

termination, and vein islets. The primary and secondary veins profused and gave rise to the ultimate veinlet. The vein islets are rectangular or squarish, small, and are distinct [9,35,36].

5.2. Stem

The transverse sections of the *E. neriifolia* stem contain stomata with a single layer of epidermis, which was covered with a well-established striated cuticle. The wider zone of hypodermis contains radially elongated and vertically arranged narrow bands of chlorenchyma and alternating parenchymatous bands. The region of the hypodermis consists of latex tubes and smaller sized oil globules. The wider region of the cortex and centrally placed parenchymatous pith is surrounded by the continuous ring of the pentagonal stellar region. The internal cells contain plenty of starch grains and have cortical zones with a large number of starch grains [37]. The region of pith is composed of thin-walled, large-sized parenchymatous cells. The stellar region is a narrow ring of angular xylem that consists of medullary rays, parenchyma rays, thin walled fibers, and 2–3 radially arranged vessels in continuation with the phloem. The pericycle is embedded, parenchymatous, and distinct with non-lignified, thick-walled, spherical fibers. The laticiferous vessels were observed with the granular latex [9].

5.3. Latex

Latex is a type of natural sap that has been reported in 10% of angiosperms. It is a mixture of proteins, alkaloids, sugars, starches, oils, tannins, resins, and gums that coagulates in exposure to air and provides defense against herbivorous insects. The latex of the *Euphorbia* species can be distinctively identified from the other species' latexes by the help of microscopy [38]. The exploration of the botanical features of laticifers discloses that laticifers are a type of specialized cells that are bound to secrete the latex. These laticifers are categorized further into two types: articulate and non-articulate [29]. The non-articulated laticifers are branched tubes with smooth, thin walls and no dividing transverse walls. The branching degree varies within the *Euphorbia* species. In the inner phloem and cortex region of the stem, the diameters of the laticifers cells are quite similar to the surrounding cells, but they become narrower towards the side of the epidermis and throughout the leaf mesophyll and pith. Unusually shaped starch grains are commonly found in laticifers of genus *Euphorbia* [39]. The latex was observed under a compound microscope and the pattern of the starch grain was found to be the most characteristic feature. Oval-shaped and dumb-bell-shaped grains were examined for *E. tirucalli* and *E. neriifolia*, whereas amoeba-shaped grains were observed in *E. antiquorum*. Additionally, a bone-shaped structure is observed commonly in these latexes but they differ in their length (50–70, 30–55, and 10–60 m in length in *E. tirucalli*, *E. neriifolia*, and *E. antiquorum*) [40,41]. The non-articulate cells are formed by the single cell enlargement, which elongate further to form a long tube of latex and divide further into non-articulate branched laticifers and non-articulate unbranched laticifers which are most commonly reported in the *Euphorbia* species [29].

6. Powder Microscopic Description

The powder is greenish yellow in color and contains fragments of epidermis with stomatal structures. The cuticle cells are striated and simple with dumb-bell-shaped starch grains and laticiferous vessels. A number of stone cells, thin and thick walled fibers, and sclereids are also present in the powder [30]. The fine powder was stained with Sudan III, iodine, and Phloroglucinol + concentrated HCl and then mounted on a slide with the help of glycerine [9]. The calcium oxalate crystals of different shapes, i.e., acicular, square, prismatic, idioblastic, and rosette, and starch grains of both types, i.e., simple and compound, were observed inside the powder of the leaf. The anomocytic stomata, with epidermal cells, xylem parenchyma, spongy parenchyma, lignified xylem fibers, starch grains (sharp angled type), multicellular trichome with a blunt tip of a unicerate nature, and schizogenous cells containing vittae-volatile were observed inside the powder of the leaf [36].

7. Properties and Actions

In Ayurveda, the rasa (taste) property of *E. neriifolia* was described as katu (pungent) and tikta; the guna (qualities) of *E. neriifolia* were described as guru, tiksha or teekshna (strong); the virya/veerya (potency) of *E. neriifolia* was described as ushna (hot); the vipaka (ripe) of *E. neriifolia* was described as katu (bitter); and karma (actions) were described as bhedana (piercing), tikshnavirecana (sharpening), and amakaphavitahara [41].

8. Ayurvedic Medicines

Many of the ayurvedic medicines include *E. neriifolia* in their formulations in order to treat different diseases [42], as shown in Table 4.

Table 4. List of some ayurvedic medicines with their actions utilizing *Euphorbia neriifolia* in their preparation.

Ayurvedic Medicines	Medicinal Uses
Abhaya lavana	Disorder of spleen and liver
Ayaskirti	Therapy of weight loss, dermal diseases, syndrome of irritable bowel, and anemia
Vishatinduka taila	Dermal skin diseases (discoloration), gout, and numbness.
Shanka dravaka	Diseases of spleen and liver, ascites, and indigestion
Agnivara Taila	Treatment of blisters and burns
Jalodarari rasa	Hepatic disorders and ascites
Ardraka ghrita	Gastritis treatment, indigestion treatment, and treatment of chronic diarrhea
Arsha kutara rasa	Hemorrhoid treatment
Madhusnuhi rasayana	Treatment of Rheumatoid arthritis, tumors, fistula, piles, diabetes, psoriasis, and skin diseases such as eczema

9. Nutritional Composition

The medicinal efficacy and pharmacological effects of an herbal drug are due to the presence of chemical constituents in it. The only thing that differentiates a remedy from a poison is its "dose". The physical composition (Table 5) of different parts of *E. neriifolia* has been widely studied [8,9,23,25,43,44]. It contains different macro- (carbohydrates, fats, and proteins) and micronutrients (magnesium, iron, chloride, sulphate, phosphate, carbonate, and nitrate). Macronutrients such as carbohydrates were observed in hydroethanol, chloroform, and ethanol extracts of *E. neriifolia* by the help of Fehling's test. The fats were reported in petroleum ether, ethanol, ethyl acetate, and hydroalcoholic extract of the leaf with the help of Millon's, Biuret, and Xanthoproteic tests. The Millon's, Biuret, and Xanthoproteic tests confirmed the presence of protein in petroleum ether, chloroform, ethyl acetate, hydroethanolic, benzene, and aqueous extract of the leaf [45]. Among the micronutrients, phosphate and chloride were observed in all parts of *E. neriifolia,* and calcium was observed only in the leaf part. Phosphorous is considered to be important for the proper functioning of the immune system, whereas chloride is an important anion in the extracellular fluid, which is involved in muscular irritability. The calcium plays a crucial role in the contraction and relaxation of blood vessels and muscles [8].

Table 5. Physiochemical analysis of different parts of *Euphorbia neriifolia*.

Plant Parts	Parameter	Value (%)	References
Leaves	Water soluble ash	4.54 ± 0.11	[8,9,23,36,43,44]
	Acid insoluble ash	0.82 ± 0.04	
	Total ash	7.36 ± 0.07	
	pH	6.1 ± 6.2	
	Moisture content	3.45 ± 0.09	
	Water soluble extractives	26.31 ± 0.12	
	Alcohol soluble extractives	14.32 ± 0.04	
	Foreign organic matter	0.87 ± 0.03	
Stem	Water soluble ash	3.042 ± 0.017	
	Acid insoluble ash	3.005 ± 0.004	
	Total ash	0.506 ± 0.015	
	pH	5.1 ± 5.5	
	Moisture content	10.8 ± 0.1	
Latex	Resinous matter	18.32%	
	pH	5.20 ± 0.17	
	Percent solid content	10.95%	
	Weight per mL	1.14 ± 0.08 gm	
	Refractive index	1.41 ± 0.12	
	Total ash value	0.315 ± 0.003	
	Water soluble ash value	1.719 ± 0.196	
	Acid insoluble ash value	1.95 ± 0.045	
	Sulfated ash value	0.147 ± 0.001	
	Moisture content	16 ± 0.057	
Bark	Water soluble ash	1.719 ± 0.196	
	Acid insoluble ash	1.95 ± 0.045	
	Total ash	0.315 ± 0.003	
	pH	5.6 ± 5.9	
	Moisture content	16 ± 0.057	

10. Medicinal Uses of Different Parts of *Euphorbia neriifolia*

Classically, *E. neriifolia* is divided into the vagbhata, susruta, and caraka categories. The caraka exhibits the properties of rasa with tikta and katu actions, and susruta shows properties of virya with the action of usna. Guna expresses snigdha, tiksna, and laghu actions. Vipaka shows the action of katu, and karma exhibits recana, dipana, and kapha-vatahara actions. The caraka displays medoroga, kusta, arsas, sotha, sula, udara, gulma, and vatavyadhi indications [46,47].

The leaves are used for carminative, stomachic, and expectorant purposes [20,48]. Flavonoids isolated from *E. neriifolia* leaf are also utilized to treat various chronic diseases, whereas oil extracted from *E. neriifolia* and sesame is utilized to treat joint pain [49]. Coronavirus disease-2019 (COVID-19) has affected the health of a large population of people all across the world. This disease has different clinical presentations. Although different medicines have been repurposed to treat COVID-19, none of them were found to be particularly effective in the perspective of the global population. Thus, there is always a need to discover novel strategies to deal with this virus. A total of 60 patients in groups of four

were analyzed properly. Approximately 66.66% of patients were below 40 years of age and approximately 68.33% were males. The patients complained of various symptoms at the commencement of therapy, such as diarrhea, red eye, loss of taste, headache, skin rash, chest pain, running nose, sore throat, difficult breathing, cough, body aches and pains, and weakness. The leaves of *E. neriifolia* were utilized for moderate and mild COVID-19 patients. The results showed the beneficent effect of *E. neriifolia* in the management of COVID-19, especially in resource-constrained and developing countries. In 15 mild COVID-19 patients, the *p*-value of the RBC variable was 0.5000 to 1.0000 from 1–7 days and 0.4493 to 0.8986 from 7–14 days; the WBC *p*-value varied from 0.0002 to 0.0004 from 1–7 days and 0.1976 to 0.3953 from 7–14 days; the neutrophil *p*-value varied from 0.0000 from 1–7 days and 0.0128 to 0.0257 on 7–14 days; the hemoglobin *p*-value varied from 0.0042 to 0.0085 from 1–7 days and 0.1032 to 0.2063 from 7–14 days; the platelet *p*-value varied from 0.0789 to 0.1578 from 1–7 days and 0.2380 to 0.4760 from 7–14 days; the d-dimer *p*-value varied from 0.0053 to 0.0105 from 1–7 days and 0.0067–0.0134 from 7–14 days; and the *p*-value of S-ferritin and oxygen saturation varied from 0.000 to 0.000 from 1–14 days. The discharge criterion was containment of COVID-19-associated symptoms so that the person can manage their health at home after being discharged from the hospital. A conclusion could not be made due to small sampling size. This plant is pertinent in the conditions of the spread of COVID-19, as the overload of CoV in infected individuals may be treated with the help of this plant without the need of hospitalization if direct connection is maintained between the physicians and the patients [50].

The latex of *E. neriifolia* is purgative, acrid, and results in dermatitis [32]. Burkill and Haniff [51] stated that *E. neriifolia* latex is a diuretic and vermifuge. The tribal people of Chattishgarh utilized the latex of *E. neriifolia* as an aphrodisiac mixture, and they treated cracks in their foot soles by boiling latex with castor oil, along with salt [52]. A chymotrypsin-like serine protease, neriifolin, was obtained from the *E. neriifolia* latex by gel filtration, cation exchange chromatography, and ammonium sulfate precipitation. The enzyme has an isoelectric point of pH 5.7 and a molecular mass of 35.24 kDa. A high ratio of proteolytic activity and stability against detergent additives, oxidizing agents, surfactants, temperature, and pH make neriifolin a suitable candidate for different applications related to industry [53]. *Euphorbia neriifolia* latex was utilized as an effective drug for rheumatism [27,54]. It was found to be useful in the treatment of the gaseous distension of the abdomen, paralysis, gout, and sciatica [54–56]. The bark was considered to be a poor stomach poison and good contact poison [9]. Other medicinal uses of *E. neriifolia* are listed in Table 6.

Table 6. The medicinal uses of *Euphorbia neriifolia*.

Plant Parts	Used in	Applications	References
Whole plant	Anemia, fever, ulcer, inflammation, loss of consciousness, piles, delirium, bronchitis, and tumor	Whole plant juice as alexipharmic, carminative, and laxative	[9]
	Vata-dosha disorders such as constipation, neuroglia, bloating, paralysis, induction of severe purgation, and for improving the strength of digestion	Whole plant	[32]
	Anal fistula	Whole plant as rubefacient and aphrodisiac	[32]
	Anorexia, fatigue, vomiting, weakness, spree syndrome, arthritis, and digestive tract disorder	Whole plant as one of the components of Dashmoolarishtam	[32]
	Insecticide	As a spray to kill insects	[57]
	For fencing	As it is covered with spines	[57]

Table 6. *Cont.*

Plant Parts	Used in	Applications	References
Leaves	Asthma	Succus administration comprising leaf juice and simple syrup in a minimum dosage of 10–20 mL three times a day	[9]
	Earache	Leaf juice	[9]
	Wound healing	Steamed leaves paste on the affected area for 4–5 days	[9,48]
	Arthritis, skin wart	Leaf juice	[49]
	Bleeding piles, ano-rectal fistula, bronchitis, cold, and cough	As a diuretic and aphrodisiac	[17]
Stem	Direct expectoration of phlegm	Stem juice at a small dosage with honey and borax	[17]
	Hydrophobia	Pulp of the stem mixed with fresh ginger	[17]
	Piles and fistula	Stem juice	[17]
	Chronic respiratory problem	Stem juice with black pepper	[57]
Latex	Drastic cathartic condition	Latex juice	[20]
	Piles	Latex juice with turmeric	[20]
	Warts	Latex juice	[51]
	Skin warts, arthritis, and earache.	Latex juice	[48]
	Opthalmia	Milky juice in combination with shoot	[20,48,58]
	Rheumatic infection	Milky juice in combination with margosa oil	[20,48,58]
	Unhealthy ulcer, glandular swelling, and scabies	EN latex juice with fresh butter	[20,48,52,58]
	Cracks in their foot soles	Boiling latex with castor oil and salt	[20,48,58]
	Wounds and burns	Milk of *E. neriifolia* latex	[20,48,58]
	Reduce swelling in piles, pain, and itching	Lukewarm extract	[20,48,58]
	Asthma	Five drops of latex juice containing gokaran root, agaba root, and madar flower with honey	[9]
	Vitiligo, fistula, and syphilis	Latex juice	[20,55,56,59]
	Leprosy, general anasarca, dropsy, syphilis, spleen and liver enlargement	Trivit root, chebulic myrobalans, long-peppers, clove soaked in latex juice for a month and then dried to form pills	[9]
	Ascites, anasarea, and tympanitis	Latex juice with chebulic myrobalan, trivit root, and long pepper	[20]
	Protection against herbivorous insects	Latex	[36]
Bark	Semen passing with urine	Mixture of bark and leaves of *Piper betle* L.	[45]

Table 6. *Cont.*

Plant Parts	Used in	Applications	References
Roots	Snake bites and scorpion stings	Root of *E. neriifolia* in combination with black pepper	[9,20,45]
	Blood pressure	A small dosage may increase blood pressure and a high dosage may decrease blood pressure	[9,20,45]
	Dropsy	Boiled mixture of root-bark in water	[9,20]

11. Phytochemical Composition

EN yielded different types of bioactive compounds that possess several biological activities. These compounds are steroidal saponins, triterpenoidal saponins, anthocyanins, alkaloids, flavonoids, several triterpenes, and sugars [20,60]. The phytochemistry of the genus *Euphorbia* is quite complex with different types of chemical compounds of various classes, as shown in Table 7.

11.1. Terpenes

The diversity of cyclic triterpenes in terms of their structure is incredible. Approximately 130 different types of triterpenoids have been isolated so far from the various species of *Euphorbia*. According to reports, tertracyclic triterpenoids are one of the major triterpenoids in the *Euphorbia* species and were divided into four classes: cycloartanes (40–84), lanostane (85–94), euphane (20–39), and tirucallane (1–19). Specifically, 9,19-cyclolanostanes (cycloartanes) are the main triterpenes that contain a cyclopropane ring and a characteristic side chain. These are the key intermediates in the biosynthesis of phytosterols and can be utilized as chemotaxic markers in the genus *Euphorbia* [61]. Thus, significant efforts were made in the isolation, characterization, and identification of novel flavonoids from the whole plant extract, stem bark, seeds, stems, roots, aerial parts, and latex of *Euphorbia* species [62]. Different types of triterpenoids, such as β-amyrin, taraxerol, Glut-5(10)-en-1-one, and Glut-5-en-3β-ol, were isolated from the leaves and stem of *E. neriifolia* [28].

Yeoh et al. [63] reported the enzyme profile of *E. neriifolia* latex and it was found to be different from the other latex containing plants. Therefore, this characteristic feature can be utilized for the identification of *E. neriifolia* from the other species of latex bearing plants. The partial purification and characterization of lectin was performed by Seshaginrao and Prasad [64], whereas a tetracyclic triterpene was isolated by Mallavadhani et al. [65]. *E. neriifolia* latex and its isolated compounds are reported to have anti-arthritic, anti-inflammatory, mitogenic, cytotoxic, pesticidal, and molluscicidal activities. The phytocompounds most related to toxicity and significant pharmacological activities in *Euphorbia* are diterpenes with ingenane, tigliane, and abietane skeletons. Latex consists of 12-deoxyphorbol esters and diterpene esters of ingenol and phorbol which are widely known to act as tumor promoting agents and highly active cocarcinogenic agents [35].

11.2. Flavonoids

Flavonoids are the other dominant phytocompound of *Euphorbia* species after triterpenoids and macrocyclic diterpenes. Flavonoids mostly present as anthocyanidins, flavanol, flavanonol, flavanone, flavonols, chalcones, neoflavonoids, and isoflavonoids. These compounds are biogenetically and structurally associated as they have chalcone as a common precursor. They are reported to have promising pharmacological activities and various therapeutic potentials. Apart from providing protection against herbivores and other pathogenic microorganisms, they act as a stress-protecting agent and are also responsible for various pharmacological activities in humans. As per different studies on *Euphorbia* species, flavonoids exhibit anti-cancer, anti-proliferative, anti-angiogenic, anti-inflammatory, anti-

diabetic, anti-microbial, anti-depressant, and anti-ulcer activities in vitro. Flavonoids are still not considered as nutrients but their consumption is found to be significant for the health of a human being. They are also utilized as natural dyes and in skin-care, and cosmetic products [66]. Several studies reported the role of flavonoids in the thyroid hormone metabolism; they are also known as vitamin P and are found to be important to deal with hemorrhage. They are considered a functional food for the prevention of diseases and promotion of good health [62].

11.3. Saponins

Saponins are functionally and structurally the biggest group of phytocompounds, commonly formed in plants, and play a very significant role in the defense mechanism of the plant. Due to their ability to produce foam when mixing with water, they are named saponin, which means "soap". Chemically, they consist of steroidal or triterpenoidal aglycones, which are associated with the different moieties of oligosaccharides. Based on the structure of aglycones, saponins are differentiated into three groups, (1) steroidal glycoalkaloids, (2) steroids, and (3) triterpenoids. Among them, triterpenes are immensely formed in licorice [67]. Crude saponin, euphol, was isolated from the hydroalcoholic extract of *E. neriifolia* and was evaluated further for various in vitro pharmacological properties. Crude saponin was reported to have a better antioxidant capacity compared to silymarin along with greater value of bitterness index. Their antioxidant ability was evaluated against hydroxyl and superoxide radicals, lipid peroxidation, reducing power, and hydrogen donating ability. The crude saponin does not show protective activity against bacteria up to 10 mg/mL of concentration, but the saponin fraction of *E. neriifolia* is found to be useful to treat inflammation, diabetes, cardiovascular diseases, and cancer [68]. The saponin fraction of *E. neriifolia* possesses hepatoprotective activity against carbon tetrachloride, aflatoxin, galactosamine, ter-butyl hydroperoxide, and cadmium, and this is because of the presence of bioactive compounds that prevent alteration in the plasma membrane of the liver and promotes repair in liver cells [69]. Other bioactive constituents that are obtained from different parts of *E. neriifolia* are shown in Table 7.

Table 7. Bioactive compounds obtained from the different parts of *Euphorbia neriifolia*.

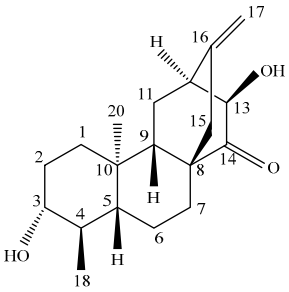
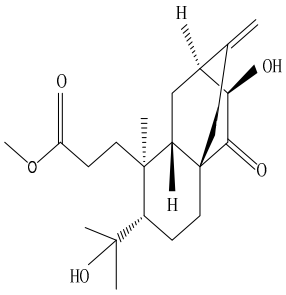
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Whole plant	Methanol extract	Diterpenoids	• Eupnerias G–I (1– 3), • Ent-16α,17-dihydroxyatisan-3-one (4), • Eurifoloid R (5), • Ent-atisane-3α,16α,17-triol (6), • Ent-atisane-3β,16α,17-triol (7), • Ent-atisane-1β,16α,17-triol (8),	 Eupnerias G  Eupnerias H	Anti-HIV effect was shown by compound 4 and 5 with EC50 values of 6.6 ± 3.2 and 6.4 ± 2.5 μg/mL, Moderate cytotoxic activity was exhibited by compound 1 and 6 against HepG2/Adr and HepG2 cells with IC_{50} values of 13.70 and 15.57 μM,	[11]

Table 7. *Cont.*

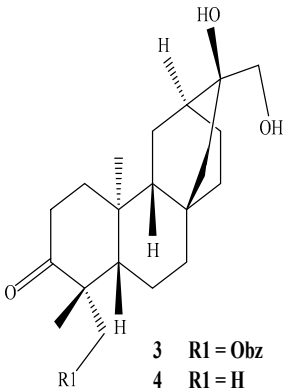
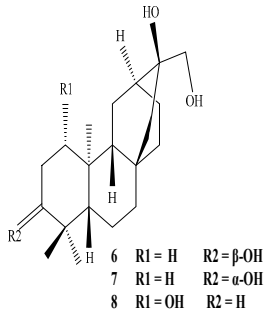
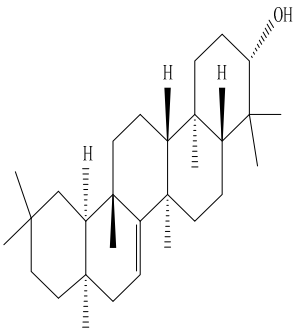
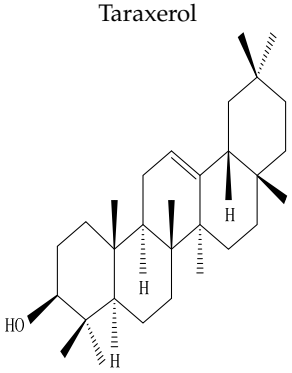
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
			• 4,13β-Dihydroxy-14-oxo-3,4-secoatis-16-en-3-oic acid methyl ester (9), • Eurifoloid M (10), • Ent-3S-hydroxyatis-16(17)-en-1,14-dione (11), • Ent-3α,13S-dihydroxyatis-16-en-14-one (12), • Ent-3β,13S-dihydroxyatis-16-en-14-one (13), • Ent-13S-hydroxyatis-16-ene-3,14-dione (14), • (4R,5S,8S,9R,10S,13R,16S)-Ent-16α,17-dihydroxy-19-tigloyloxykauran-3-one (15)	 Eupnerias I, ent-16α,17-dihydroxyatisan-3-one, Eurifoloid R  Ent-atisane-3α,16α,17-triol, Ent-atisane-3β,16α,17-triol, Ent-atisane-1β,16α,17-triol	and compound 15 was reported to exhibit cytotoxic activity (IC_{50} = 0.01 μM) against HepG2 but not against HepG2/Adr cell line	
Whole plant	Hexane extract	Triterpene and Triterpene alcohol	• Taraxerol, and • β-Amyrin	 Taraxerol  β-Amyrin	Taraxerol exhibits anti-cancer activity via Nf-kB signalling pathway inhibition or by induction of apoptosis in case of middle ear epithelial cholesteatoma cells	[70,71]

Table 7. *Cont.*

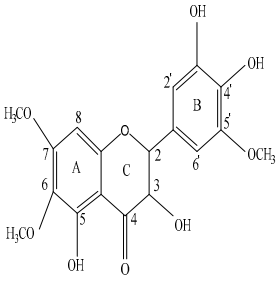
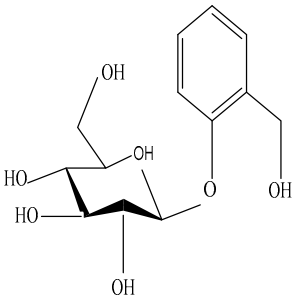
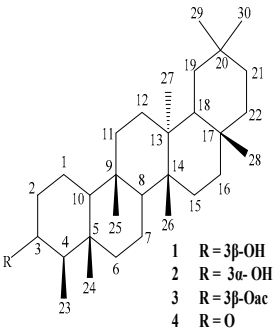
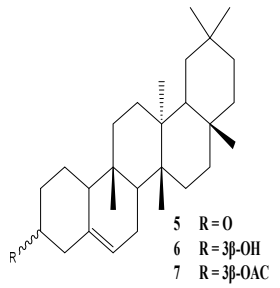
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Leaves	Hydroethanolic extract	Flavonoids	• 2-(3,4-Dihydroxy-5-methoxy-phenyl)-3,5-dihydroxy-6,7-dimethoxychromen-4-one ($C_{18}H_{18}O_9$)	 2-(3,4-dihydroxy-5-methoxy-phenyl)-3,5-dihydroxy-6,7-dimethoxychromen-4-one ($C_{18}H_{18}O_9$)	Exhibits anti-cancer activity due to its ability to scavenge reactive oxygen species and to inhibit lipid peroxidation	[66]
Leaves	Ethanolic extract		• Glycosides	 Glycosides	Inhibits the proliferation of *Plamodium falciparum* with IC_{50} values of 5.4, 4.1, and 1.1 µg/mL, and shows cytotoxic activity against KN3-1 human epidermoid cancer cells	[72]
Leaves	Ethanolic extract	Triterpenoids • (1–4) friedelane • (5–7) glutinane • (8) Lupane • (9–11) Taraxerane • (12,13) Oleanane • (14) Dammarane • (15) Ocotillone	• 3β-Friedelanol (1), • 3α-Friedelanol (2), • 3β-Acetoxy fridelane (3), • Friedelin (4), • Glutinone (5), • Glutin-5-en-3β-ol (6), • Glutinol acetate (7), • Lupenone (8), • Epitaraxerol (9), • Epitaraxeryl acetate (10), • Taraxeryl acetate (11), • β-amyrin (12),	 3β-Friedelanol, 3α-Friedelanol, 3β-Acetoxy fridelane, Friedelin  Glutinone, Glutin-5-en-3β-ol, Glutinol acetate	Triterpenoids showed anti-viral activity in comparison to actinomycin D, Found to be effective against the herpes virus and inhibits replication of SARS-COV by binding to its 3CL pro proteases	[28,57,72]

Table 7. *Cont.*

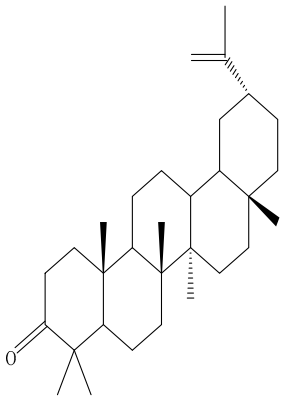
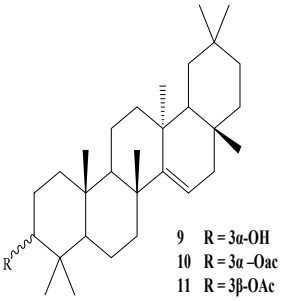
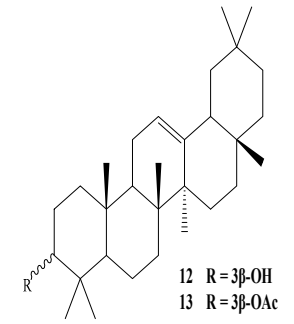
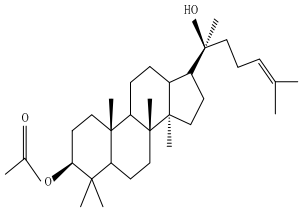
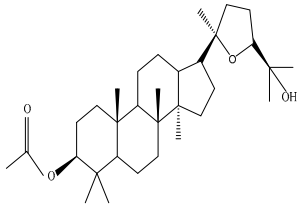
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Lupenone		
		• (16,17) Simiarenane • (18–20) Cycloartane • (21 & 22) Cycloeucalane	• β-amyrin acetate (13), • Dammarenediol II acetate (14), • Cabraleadiol monoacetate (15), • 3β-Simiarenol (16), • Simiarenone (17), • Cycloartenol (18), • 24-Oxocycloart-25-en-3β-ol (19), • (23Z)-Cycloart-23-ene-3β,25-diol (20), • Cycloeucalenol (21), • 29-Norcycloartanol (22), and • Afzelin (23)	 Epitaraxerol, Epitaraxeryl acetate, Taraxeryl acetate		
				 β-Amyrin, β-Amyrin acetate		
				 Dammarenediol II acetate		
				 Cabraleadiol monoacetate		

Table 7. *Cont.*

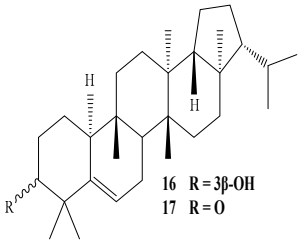
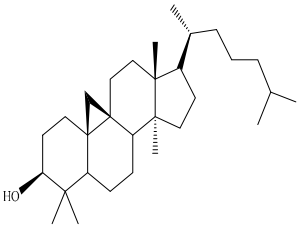
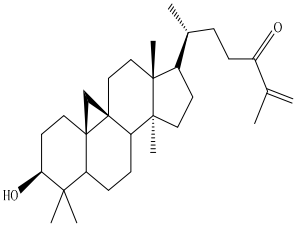
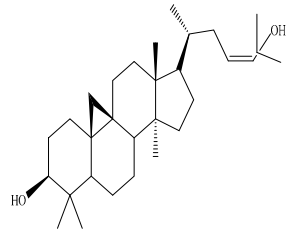
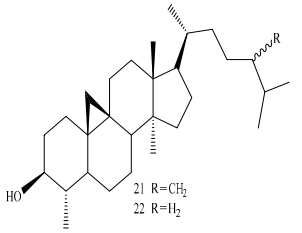
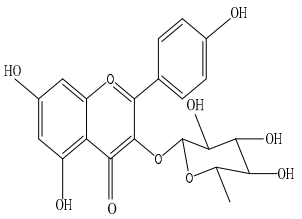
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 3β-Simiarenol, Simiarenone	
				 Cycloartenol	
				 24-Oxocycloart-25-en-3β-ol	
				 (23Z)-Cycloart-23-ene-3β,25-diol	
				 29-Norcycloartanol	
				 Afzelin	

Table 7. *Cont.*

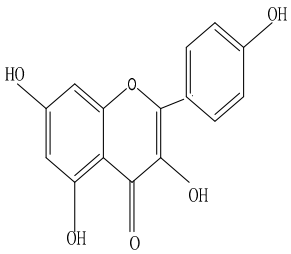
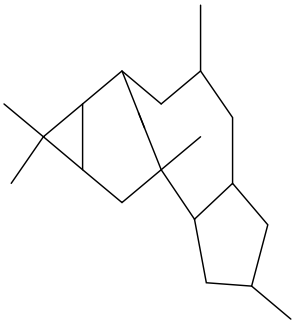
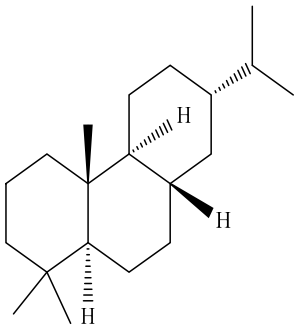
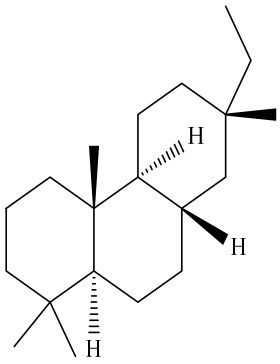
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Leaves	Aqueous extract	Flavonoid	• Kaempferol	 Kaempferol	Kaempferol modulates metastasis, inflammation, angiogenesis, and apoptosis, and provides protection against chronic diseases by activating the body antioxidant defense mechanism against free reactive species	[73,74]
Leaves	Ethyl acetate extract	Diterpenoids (Eurifoloids A–R)	• Ingenane (1&2), • Abietane (3–7), • Isopimarane (8–12), and • ent-atisane (13–18)	 Ingenane (1&2)  Abietane  Isopimarane	Various diterpenoids such as ingenanae, abietane, isopimarane, and ent-atisane exhibit anti-HIV activity	[75]

Table 7. *Cont.*

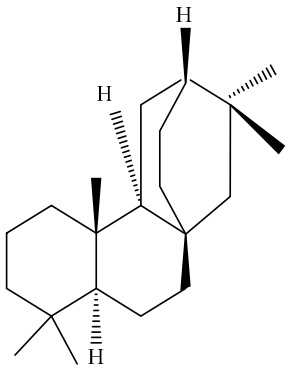
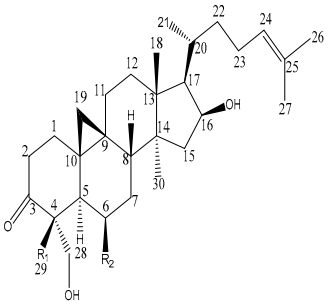
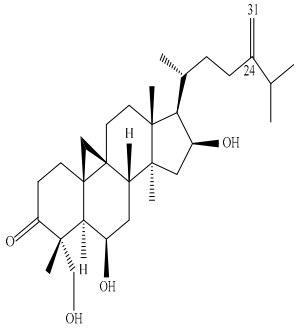
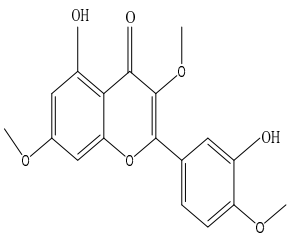
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Ent-atisane		
Leaves	Methanol extract	Cycloartane terpenoids	• Neriifolins A–C	 **R_1** = CH_3; **R_2** = OH **R1** = CH_2; **R_2** = H Neriifolins A, Neriifolins B  Neriifolins C	Neriifolins A–C showed cytotoxicity against MCF breast cancer cell line with IC_{50} value of 9.50, 7.12, and 13.14 µM	[76]
Leaves	Methanol extract	Pachypodol	• 5,40-Dihydroxy-3,7,30-trimethoxyflavone	 5,40-Dihydroxy-3,7,30-trimethoxyflavone	Inhibits the proliferation of *Psudomonas aeruginosa*, *Escherichia coli*, *Streptococcus faecalis*, *Streptococcus aureus*, *Bacillus subtilis*, *Candida glabrata*, *Candida krusei*, and *Candida albicans*	[57]

Table 7. *Cont.*

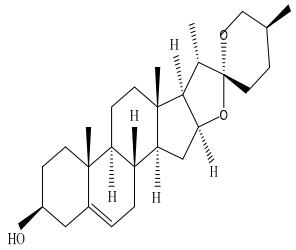
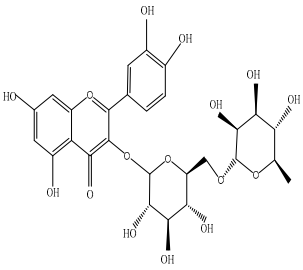
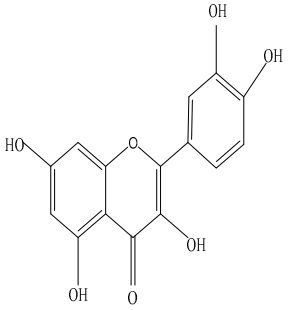
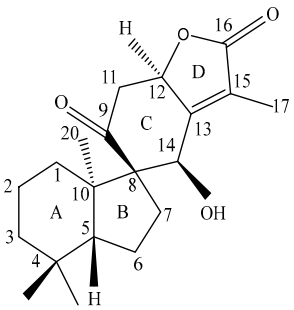
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Leaf	Chloroform and ethanol extract		• Saponin (Sapogenin), • Rutin, and • Quercetin	 Saponin  Rutin  Quercetin	Saponin shows anti-microbial activity against *Staphylococcus aeruginosa*, *Escherichia coli*, and *Pseudomonas aeruginosa;* Rutin inhibits the activity of *Cryptococcus gattii*, and *Cryptococcus neoformans;* and Quercetin found to be effective against *Candida albicans*	[9,57,69, 77,78]
Leaves	_	Diterpenoids	• Phorneroids A–M, and three known compounds	 Phorneroids A	Phorneroids A–M, and three known compounds exhibit moderate cytotoxic activity against HL-60 and A549 cancer cell line	[79]

Table 7. *Cont.*

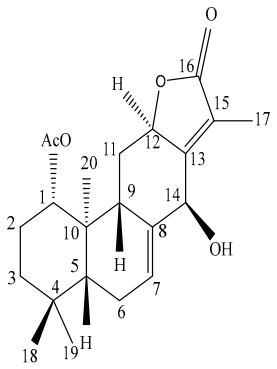
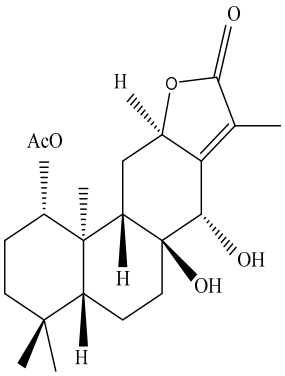
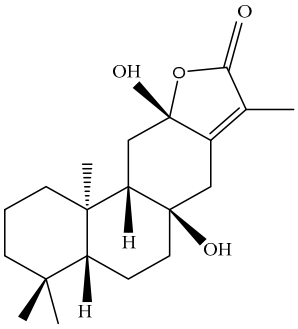
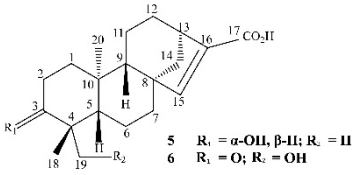
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Phorneroids B		
				 Phorneroids C		
				 Phorneroids D		
				 **5** R_1 = α-OH, β-H; R_2 = H **6** R_1 = O; R_2 = OH Phorneroids E, F		

Table 7. *Cont.*

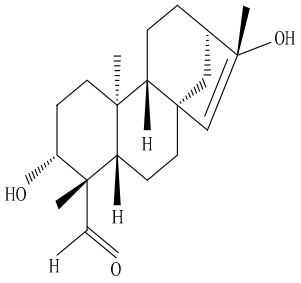
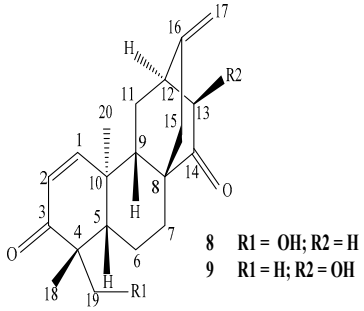
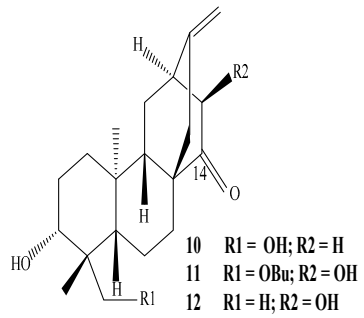
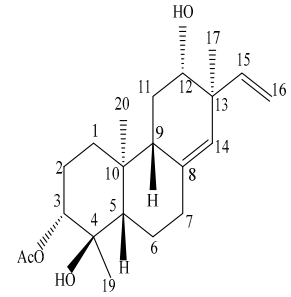
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Phorneroids G		
				 **8** R1 = OH; R2 = H **9** R1 = H; R2 = OH Phorneroids H, I		
				 **10** R1 = OH; R2 = H **11** R1 = OBu; R2 = OH **12** R1 = H; R2 = OH Phorneroids J, K, L		
				 Phorneroids M		

Table 7. *Cont.*

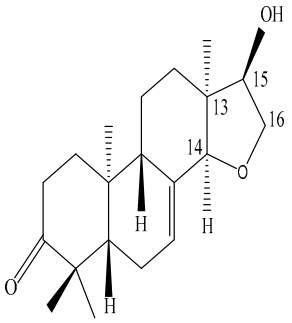
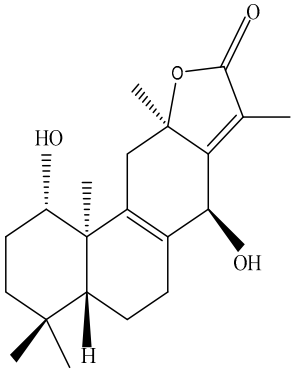
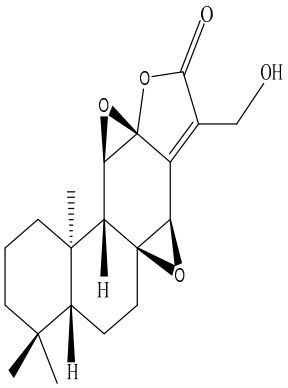
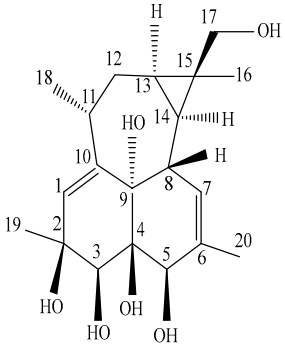
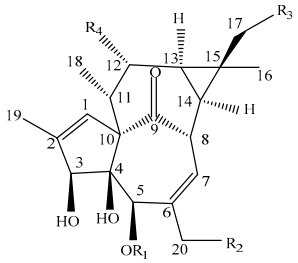
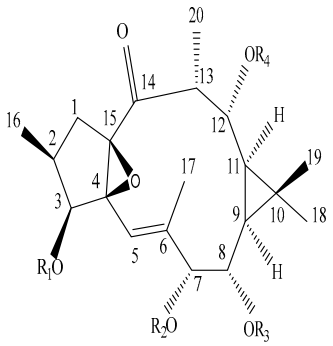
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Compound I		
				 Compound II		
				 Compound III		
Leaves	_	Ingenane and ingol diterpenoids	• Phonerilins A–K, and five known analogues	 Phonerilins A	Phonerilins A–K, and five known analogues exhibit moderate cytotoxic activity against HL-60 and A549 cancer cell line	[80]

Table 7. *Cont.*

Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
						

	R1	R2	R3	R4
2	H	OH	H	OH
3	H	OH	H	Oac
4	H	OH	OH	H
5	Ang	H	OH	H
6	H	H	OH	H
12	H	H	OH	H
13	H	OAc	H	H

Phonerilins B, Phonerilins C, Phonerilins D, Phonerilins E, Phonerilins F, Phonerilins G, and 2 analogues



	R1	R2	R3	R4
7	H	H	Ac	Ac
8	H	H	MeBu	Ac
9	Ac	Ac	A	Ac
10	Ac	Ac	B	Ac
14	H	H	H	H
15	H	Ac	Tig	Ac
16	H	H	Me	Ac

Phonerilins G, Phonerilins H, Phonerilins I, Phonerilins J, Phonerilins K, and three analogues

Table 7. *Cont.*

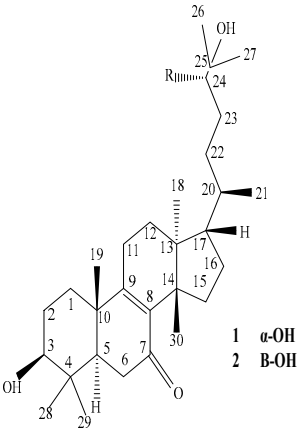
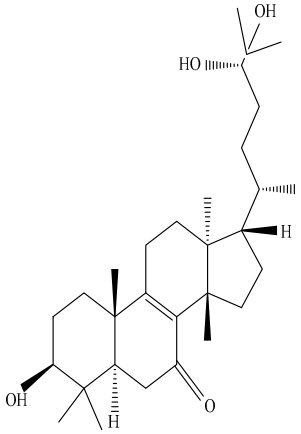
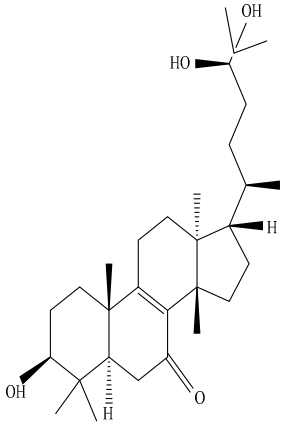
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Stem	Ethanolic extract	Euphane and tirucallane triterpenes	• Neritriterpenols A–G, and four known triterpene	 Neritriterpenols A, Neritriterpenols B  Neritriterpenols C  Neritriterpenols D	Neritriterpenols A–G, and four known triterpene exhibit anti-proliferative and anti-inflammatory activities	[12]

Table 7. *Cont.*

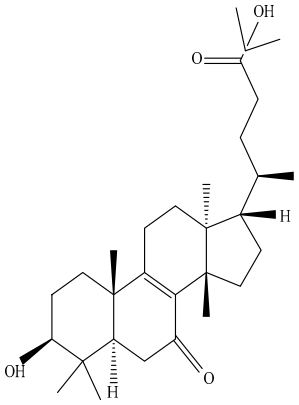
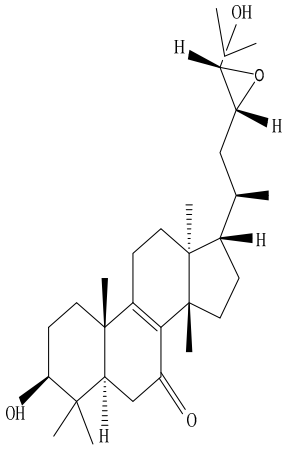
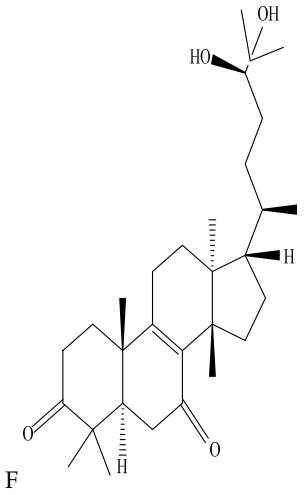
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Neritriterpenols E		
				 Neritriterpenols		
				 F Neritriterpenols G		

Table 7. *Cont.*

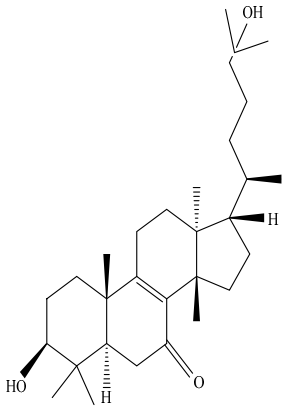
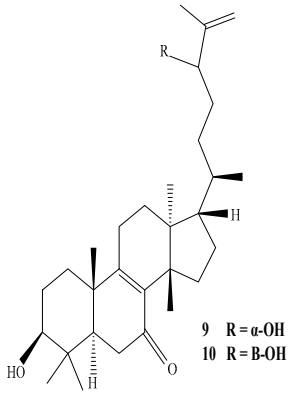
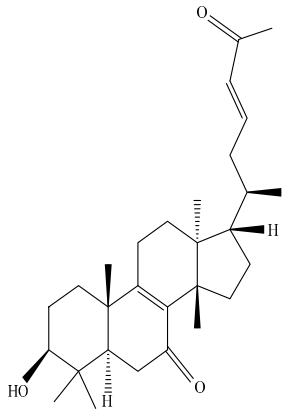
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
				 Triterpene		
				 Triterpenes		
				 Triterpenes		

Table 7. *Cont.*

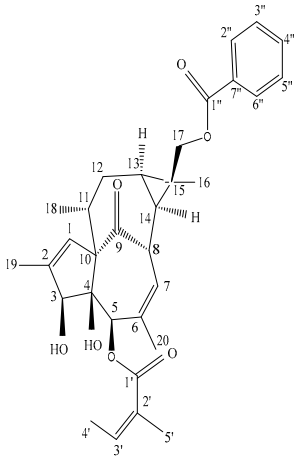
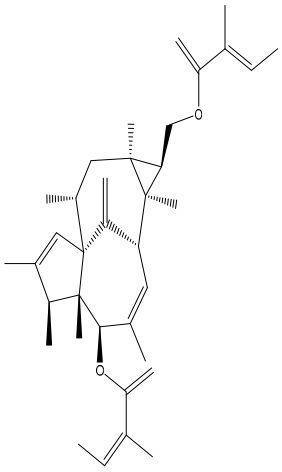
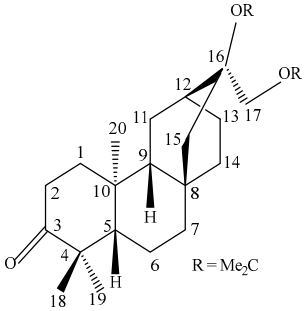
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Stem bark	Ethyl acetate extract	Ingenane-type diterpenoids	• Eurifoloid E, and • Euphorneroid A	 Eurifoloid E  Euphorneroid A	Eurifoloid E and Euphorneroid A inhibit pro-inflammatory mediators such as iNOS, IL-6, IL-1β, and NO in cases of LPS-induced RAW264.7 macrophage	[81]
Stem bark	Methanol extract	Diterpenes	• Ent-3-oxoatis-16α,17-acetonide (4),	 Ent-3-oxoatis-16α,17-acetonide	Exhibits anti-HIV activity with EC_{50} value of 8.7 μg/mL	[82]

Table 7. *Cont.*

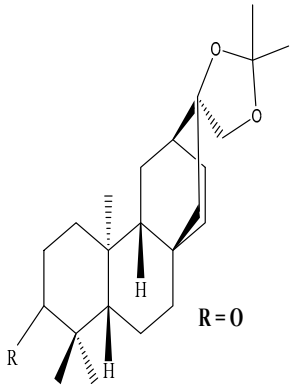
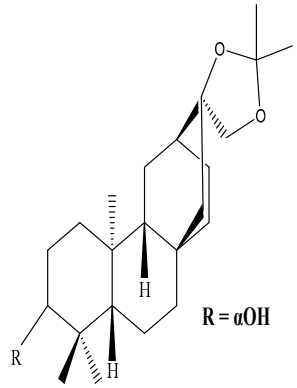
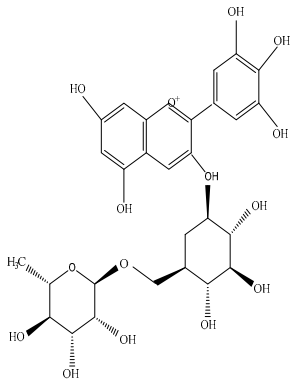
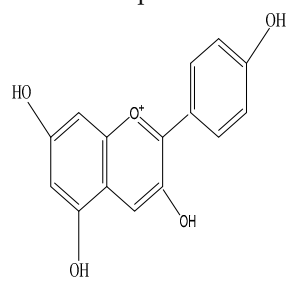
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Stem and Bark	Methanol extract	Diterpenes	• Ent-3-oxoatisan-16α, 17-acetonide, and • Euphorneroid D	 Ent-3-oxoatisan-16α, 17-acetonide  Euphorneroid D	Ent-3-oxoatisan-16α, 17-acetonide and Euphorneroid D exhibit anti-HIV activity with EC_{50} value of 24 and 34 mM	[83]
Stem and Bark	Ethanol and petroleum ether extract	Anthocyanin	• Tulipanin, and • Pelargonin	 Tulipanin  Pelargonin	Tulipanin inhibits the proliferation of *Bacillus subtilis*, *E. coli*, *P. aeruginosa*, and *Staphylococcus aureus*	[57,70]

Table 7. *Cont.*

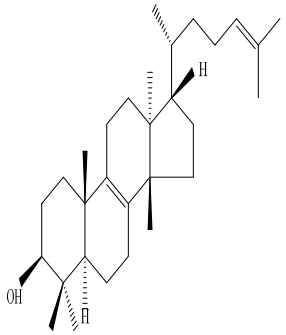
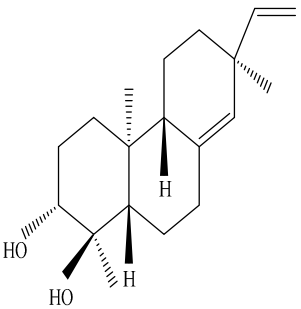
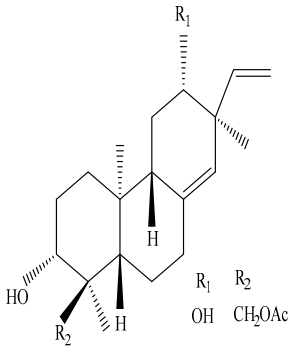
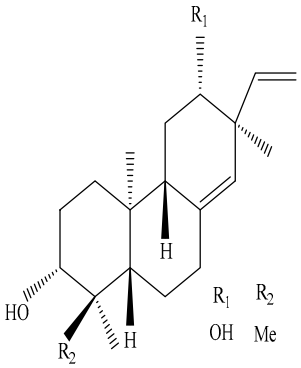
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Stem and Bark	Methanol extract	Triterpene alcohol	• Euphol	 Euphol	Euphol exhibits an anti-nociceptive effect in neuropathic pain and inflammatory conditions	[70,84]
Stem barks	Ethyl acetate extract	Ent-isopimarane diterpenoids	• Eupneria J, • Eurifoloid H, and • Ent-isopimara-8(14),15-dien-3β,12β-diol	 Eupneria J  Eurifoloid H  Ent-isopimara-8(14),15-dien-3β,12β-diol	Eupneria J, Eurifoloid H, and ent-isopimara-8(14),15-dien-3β,12β-diol exhibit anti-HIV activity with an IC_{50} value of 6.70 and 0.31 µg/mL and anti-influenza activity with an IC_{50} value of 3.86 µg/mL	[85]

Table 7. *Cont.*

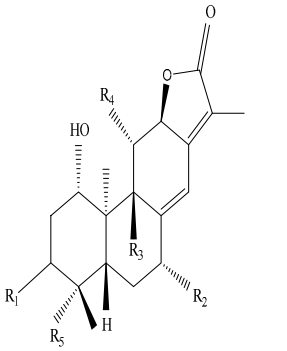
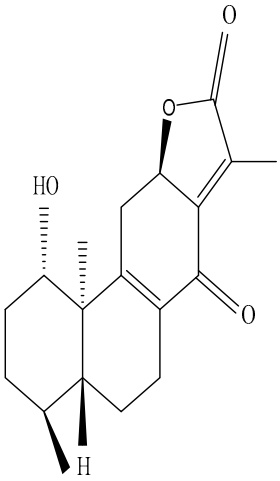
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Stem bark	Ethyl acetate extract	Ent-abietane diterpenoids	• Eupnerias A–F	 R1 R2 R3 R4 R5 1 H H H OH Me 2 H OH H H Me 3 H H H H CH2OH 4 H H OH H Me 5 βOH H H H Me Eupnerias A–E  Eupnerias F	Exhibit anti-influenza and anti-inflammatory activities	[86]

Table 7. *Cont.*

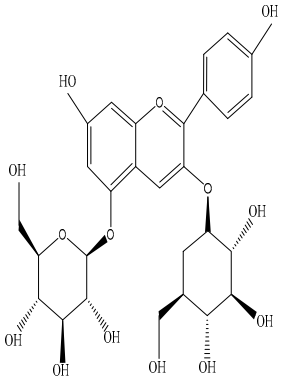
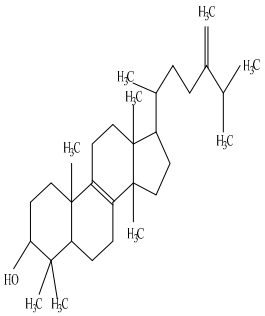
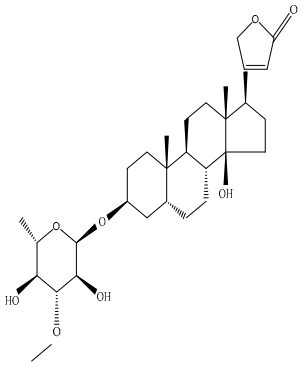
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Bark	Petroleum ether extract	Diterpenes	• Pelargonin-3,5-diglucoside, • n-Hexacosanol, and • Euphorbol	 Pelargonin-3,5-diglucoside  n-Hexacosanol  Euphorbol	n-Hexacosanol was found to be effective to treat diabetic ileum by ameliorating the overexpression of M(3) and M(2) mRNA receptor	[70,87]
Fresh Latex from stem	Crude extract		• Neriifolin-S	 Neriifolin-S	Neriifolin-S exhibits milk clotting activity	[53]

Table 7. *Cont.*

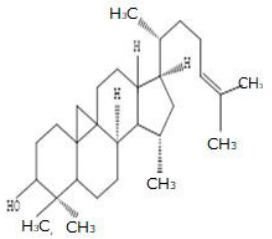
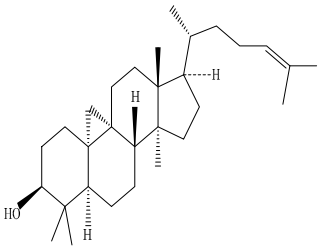
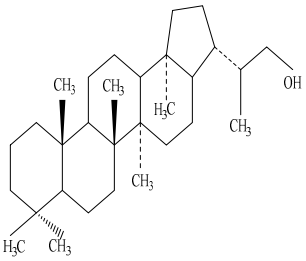
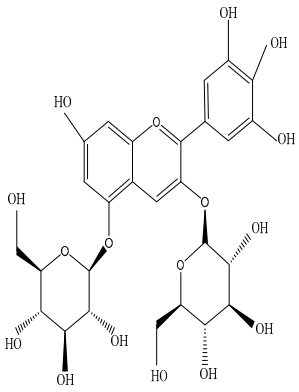
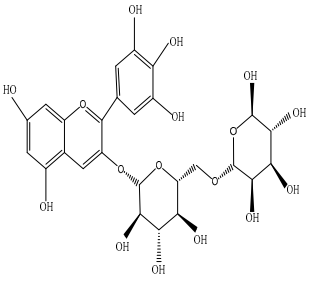
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Dried Latex	Methanol extract	Triterpene and Triterpene alcohol	• Cycloartenol ($C_{10}H_{50}O$), • Nerifolione [9,19-cyclolanost-20(21)-en-24-ol-3-one], and • Nerifoliol	 Cycloartenol  Nerifolione  Nerifoliol	Cycloartenol, Nerifolione, and Nerifoliol inhibit p38 MAP kinase phosphorylation and migration of glioma cells	[60,70,88]
Root	Petroleum ether extract	Diterpenes	• Delphin, and • Tulipanin	 Delphin  Tulipanin	Delphinidin 3,5-O-diglucoside and Tulipanin exhibit antioxidant activity by suppressing the formation of reactive oxygen species from lacrimal gland tissue that preserves tear secretion	[70,89,90]

Table 7. *Cont.*

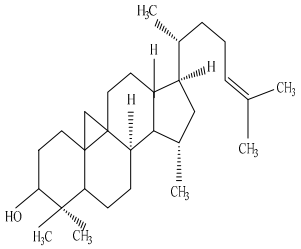
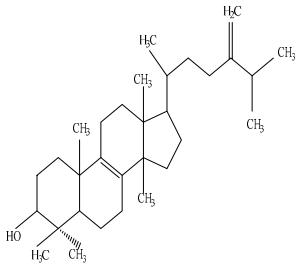
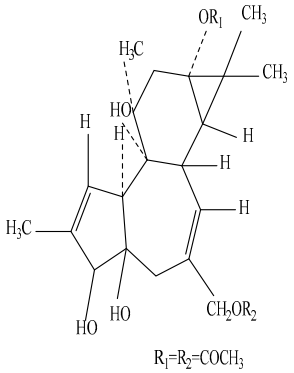
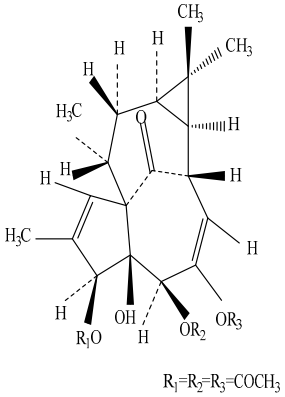
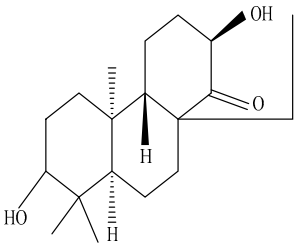
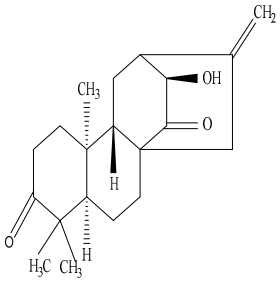
Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Root	Ethanol extract	Triterpene alcohol	• Cycloartenol, and • Euphorbol	 Cycloartenol  Euphorbol	Cycloartenol exhibits antioxidant activity	[70,91]
Root	Methanolic extract	Diterpenes	• 12-Deoxyphorbhol-13, 20-diacetate, and • Ingenol triacetate	 R_1=R_2=$COCH_3$ 12-Deoxyphorbhol-13, 20-diacetate  R_1=R_2=R_3=$COCH_3$ Ingenol triacetate	12-Deoxyphorbhol-13, 20-diacetate and Ingenol triacetate exhibit anti-HIV activity in the case of MT-4 cells at 0.65 and 0.051 mM concentration, and are useful to treat the skin condition, actinic keratosis	[70,92,93]

Table 7. *Cont.*

Plant part	Extracts	Secondary Metabolite	Types	Structure	Pharmacological Activity	References
Fresh Root	Protease fraction	Diterpenes	• Neriifolene [($C_{20}H_{30}O_3$), and • Atisine diterpene anti-quorin ($C_{20}H_{28}O_3$)	 Neriifolene  Atisine diterpene anti-quorin	Atisine diterpene anti-quorin exhibits wound healing activity by inducing the intercellular signaling and aggregation of platelets vis PAR-1	[70,94]

12. Pharmacological Actions of *Euphorbia neriifolia*

Various pharmacological activities were reported from different parts of *E. neriifolia* including antioxidant, anti-diabetic, immunomodulatory, anti-inflammatory, anti-arthritic, wound healing, anti-atherosclerosis, radioprotective, anti-anxiety, anti-convulsant, anti-psychotic, anti-thrombotic, dermal irritation, hemolytic, death receptor expression enhancing, analgesic, anti-diuretic, anti-ulcer, anesthetic, anti-bacterial, anti-fungal, anti-viral, anti-venom, anti-diarrheal, antifertility, fish stupefying, pesticidal, abscess, and anti-cancer activity.

12.1. Antioxidant Property

Plants are the natural reservoir of phytocompounds of antioxidant activity. These compounds play a crucial role in plant adaptation and acclimation to environmental changes and are also useful for human health [95]. Plants cannot escape from anthropogenic practices such as pollution, habitat destruction, etc. and from natural origin practices such as pests, soil composition, water availability, and temperature. These practices disturb the balance maintained between scavenging and production of ROS, which further results in the induction of oxidative stress [95]. This stress causes considerable damage to different components of cells, thereby activating various cell deaths and cell survival pathways or impaired normal functioning of cell [96].

To prevent this damage, the plant has some metabolites and enzymes. Glutathione (GSH) and ascorbate are water-soluble metabolites but they also contain secondary metabolites such as terpenoids, flavonoids, and polyphenols that participate in counteracting the ROS under different stress conditions [97–99]. Most of the phytocompounds possess biological activities against microorganisms that form a basis for their medicinal use [95]. Damage caused due to free reactive species is a major factor responsible for the cause of different degenerative ailments such as cancer and ageing, as shown in Figure 2 [100]. Sapogenin, especially the euphol, showed antioxidant activity by acting as a donor of an electron. It inhibits the ROS that were derived from superoxide and hydroxyl free radicals with great potential [68]. Cycloartenol isolated from *E. neriifolia* showed greater scavenging activity at a concentration of 40 µg/mL. It inhibited the lipid peroxidation at a concentration of 10–100 µg/mL with % inhibition ranging from 34.56–72.87% [91].

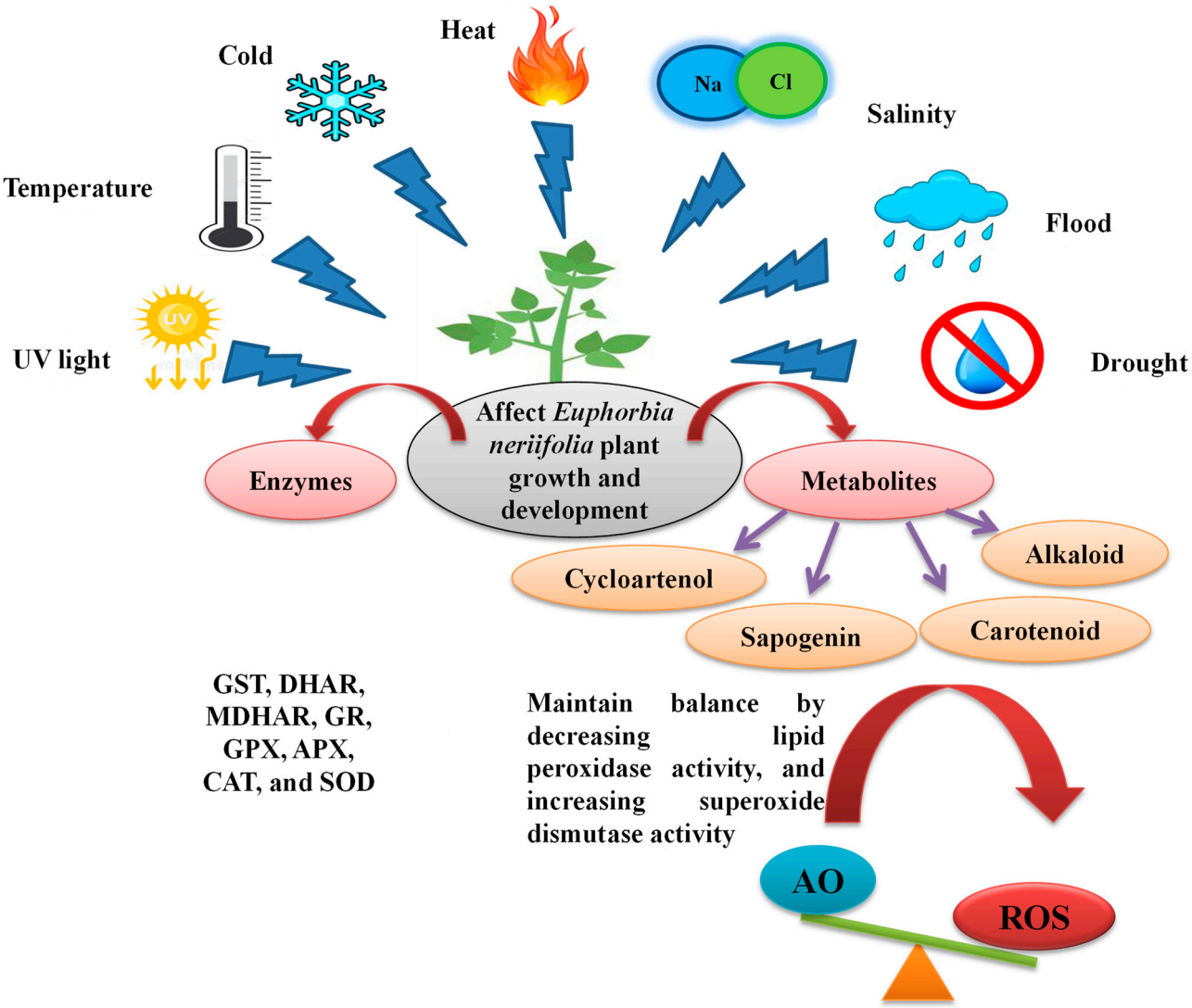


Figure 2. Effect of abiotic stress and plant metabolites on the reactive oxygen species (ROS). (GST: glutathione transferase; DHAR: dehydroascorbate reductase; MDHAR: monodehydroascorbate reductase; GR: glutathione reductase; GPX: glutathione peroxidase; APX: ascorbate peroxidase; CAT: catalase; SOD: superoxide dismutase; AO: antioxidant; ROS: reactive oxygen species).

12.2. Anti-Diabetic Potential

Diabetes mellitus is a main reason for mortality and morbidity in the human population. It is a common problem among the Indian people and it is expected to affect approximately 134 million people worldwide by 2045 [47]. This disease is characterized by polyuria, polydipsia, and hyperglycemia, and causes complications in the nerves, kidneys, and eyes. This disease is also related to the high incidence of cardiovascular diseases. Insulin therapy, oral hypoglycemic drugs, exercise, and diet are some of the therapeutic options for diabetes. Other complementary treatments include plant derived drugs, which are considered to be free from any type of harmful effects and less toxic than the synthetic ones, as shown in Figure 3 [101]. Different extracts of *E. neriifolia*, such as ethanolic and methanolic extract, were found to be effective in the control of blood glucose levels in the experimental model rat. Different parameters, such as suppressed serum lipid levels; suppressed oral glucose tolerance; inhibition of pro-inflammatory chemicals (iNOS and COX-2); expression of chemokines (CCL8 and CCL4); transformation of T-lymphocytes to T-helper cells; expression of cytokines such as TNF-α, IL-6, 8, and INF-γ; stimulation of signaling molecules (ERK, p38, JNK, NF-kB); activation of immune cells; and suppressed

levels of fasting blood glucose were found to be observed in response to *E. neriifolia* extracts [102–104].

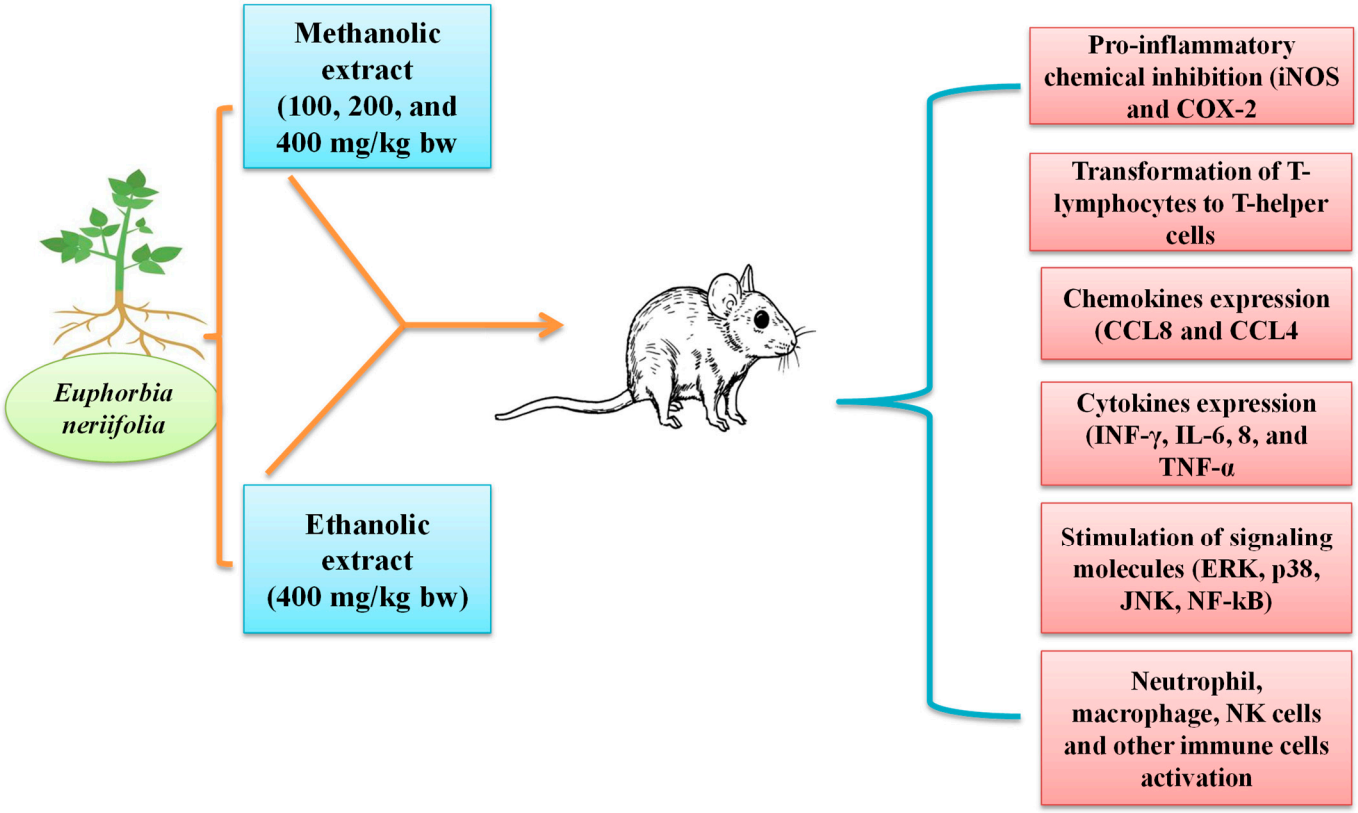


Figure 3. Anti-diabetic potential of the plant extract. [iNOS: inducible nitric oxide synthase; COX-2: cyclooxygenase-2; CCL8: chemokine (C-C motif) ligand 8; chemokine (C-C motif) ligand 4; INF-γ: interferon-gamma; IL-6; interleukin 6; TNF-α: tumor necrosis factor alpha; ERK: extracellular signal-regulated kinase; p38: mitogen-activated protein kinase; JNK: Jun N-terminal kinase; NF-kB: nuclear factor kappa B; NK: natural killer cells].

12.3. Immunomodulatory Effect

In the traditional medicine system, various plants are utilized as ingredients of formulations and are applied as adaptogens and tonics for the treatment of rheumatism, immunological disorders, and chronic infections [105]. Plant extracts are most commonly prepared in ethanol and water, which leads to the isolation of hydrophobic and hydrophilic compounds [106]. Water soluble plant polysaccharides activate (+) the responses of the immune system, whereas terpenoids and flavonoids commonly inhibit (-) the responses of the immune system. In some cases, water soluble polysaccharides are converted into short chain fatty acids of a hydrophobic nature that results in anti-inflammatory and systematic effects on the host [107]. The gut microbiota involves a large population of bacteria that is present in the large and small intestines of animals and is determined to take part in different physiological processes such as immunological reactions. Dietary type polysaccharides isolated from mushrooms or any plant species are large sized molecules and are not easily absorbed by the gut mucosa. Remaining undigested polysaccharides reach the large intestine and are digested by the bacterial population to produce short chain fatty acids (SCFAa) such as propionate, butyrate, and acetate. These SCFAs are responsible for anti-inflammatory effects in the host and are found to be responsible for the various advantageous effects of dietary fiber and polysaccharides [107].

Herbal agents are considered an alternative approach to modern medication; consequently, immunomodulatory agents from plants have proven to be an effective and

safe approach [108]. These natural immunomodulators stimulate the natural defenses of the body to fight against pathogenic microorganisms such as viruses by maintaining an immune system homeostasis. Imbalances or malfunctions in the immune system are related to different chronic diseases such as viral infection, autoimmune disorders, inflammatory bowel disease, cancer, and allergies. Polysaccharides, organosulfur-containing compounds, polyphenols, flavonoids, terpenoids, and carotenoids are valuable phyto constituents with known chemical structures and potent immunomodulating activities, as shown in Figure 4 [109].

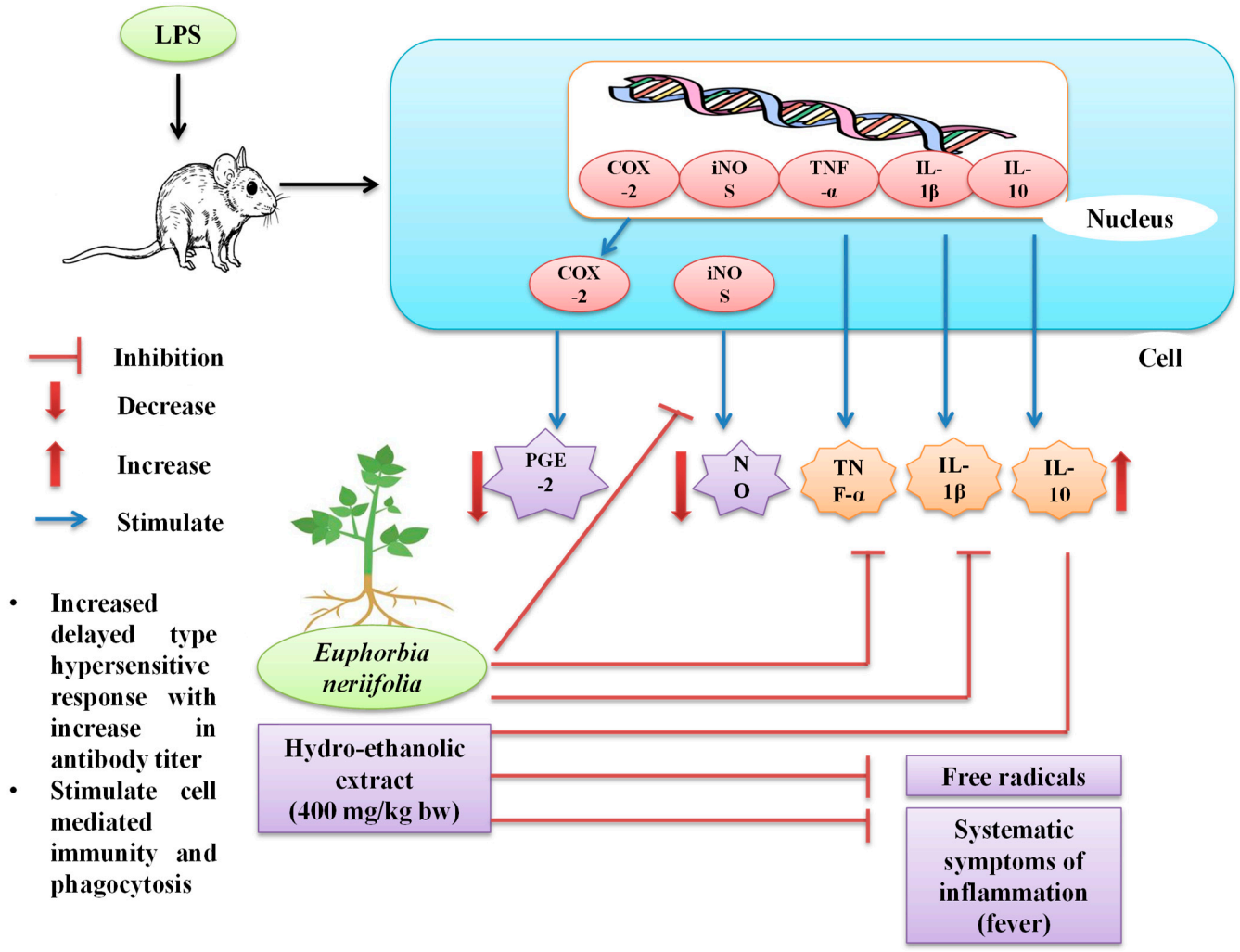


Figure 4. Immunomodulatory mechanism shown by the medicinal plant. (LPS: lipopolyssacharides; COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; TNF-α: tumor necrosis factor-alpha; IL-1β: interleukin-1beta; IL-10; interleukin 10; PGE2: prostaglandin E2).

The immunomodulatory activity of hydro-alcoholic extract of *E. neriifolia* leaf was assessed by determining the rat's survival against *E.coli*-induced abdominal sepsis. This activity was determined based on the specific and nonspecific immune response, including tests such as estimation of antibody titer, delayed type hypersensitivity, carbon clearance test, and survival study. The treatment of *E. neriifolia* at 400 mg/kg provided protection against *E. coli*-directed abdominal sepsis for 15 days after infection. Treatment with the extract for 14 days significantly ($p < 0.01$) raised the count of lymphocytes and showed better phagocytic potential.

The extract treatment significantly ($p < 0.05$) increased the delayed type of hypersensitive reaction against sheep red blood cells (SRBC) in rats at 24 and 48 h (20.63% and 12.24%).

It also potentiated the humoral immune response that resulted in the increase in antibody titer (270.88%) at 400 mg/kg dose on 21 days of treatment. It inhibited the expression of iNOS, TNF-α, and IL-1β and stimulated the expression of Cox-2 and IL-10 to restrict the free radicals and systematic symptoms related to inflammation. Thus, *E. neriifolia* was found to be a strong immunostimulant as it stimulated cell-mediated immunity and phagocytosis [110].

12.4. Anti-Inflammatory Properties

Inflammation includes redness of skin with fever and pain at the inflamed site. The major steps involved in inflammation are (i) increased vascular permeability, (ii) leucocyte infiltration, and (iii) formation of a granuloma. Inflammation is the defense of a host organism against harmful stimuli [111]. This process must be in a controlled manner since its uncontrolled mechanism may result in pathophysiological disorders such as cancer. The typical process of inflammation in the initial stage is marked by an acute phase where a series begins with the primary response of the vascular and immune system right after damage or infection to tissues. This phase remains for a short time, basically before the establishment of the immune response [99]. Macrophages play a crucial role in fighting against infectious diseases and participate in the body repair mechanism based on their immune activation and powerful phagocytosis effects. Different macrophages precisely regulate and mutually transform with the microenvironmental changes to maintain the homeostasis condition. Classical macrophages secrete chemokines and inflammatory cytokines, which have a potent phagocytic function and an important role in the immune defense. Excessive activation of these macrophages results in the secretion of a large number of cytokines that cause tissue damage and ultimately results in autoimmune diseases [111].

Alternatively, activated macrophages promote tissue recovery, wound healing, and increase the inflammatory response but cancer cells may take advantage of this, leading to immune escape. Therefore, it is important to study the regulation of macrophage function that is related to immune homeostasis, immune defense, and the treatment of different diseases. Chronic inflammation brings a shift in the type of cells that are present at the inflammatory site and is determined by the simultaneous healing and destruction of tissue from the inflammatory process. Pain is a typical response, which may be due to bodily harm, inflammation, or as the result of unpleasant awareness of a noxious stimuli [112]. Acute inflammation is a homeostatic mechanism that provides benefits to the host though the repair mechanism. Carrageenan-directed paw-edema is one of the old models to evaluate the acute anti-inflammatory agents. Its injection in rats includes two phases. The early phase is characterized by the release of bradykinins, serotonin, and histamine and it lasts for an hour only. The late phase begins just after the early phase, in which mediators are released by the early phase, leading to the activation of neutrophil infiltration and the further release of cyclooxygenases, forming prostaglandins. Tumor necrosis factor-α (TNF-α), nitric oxide (NO), and interleukin-1β (IL-1β) are some of the mediators that affect the late phase of inflammation. The persistence of late-phase mediators propagates inflammation to the chronic stage, which is associated with inflammatory diseases, as shown in Figure 5 [113].

The induction of histamine, serotonin, and lipopolysaccharides are related to inflammation. LPS activates cellular responses that further stimulate natural or innate immunity. Serotonin regulates the cell proliferation and inflammation that are modulated by macrophages. Histamine also promotes the regulatory and inflammatory responses that are associated with pathogenic diseases [114]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the class of analgesic and anti-inflammatory drugs that alleviates the symptoms related to inflammation by restricting COX. Unfortunately, these drugs have significant side effects on the renal system, blood coagulation, and the gastrointestinal lining due to the restriction of the housekeeping enzyme COX-1. However, some COX-2 inhibitors are free from these side effects. Thus, alternative agents with no side effects and potent activity are needed [115].

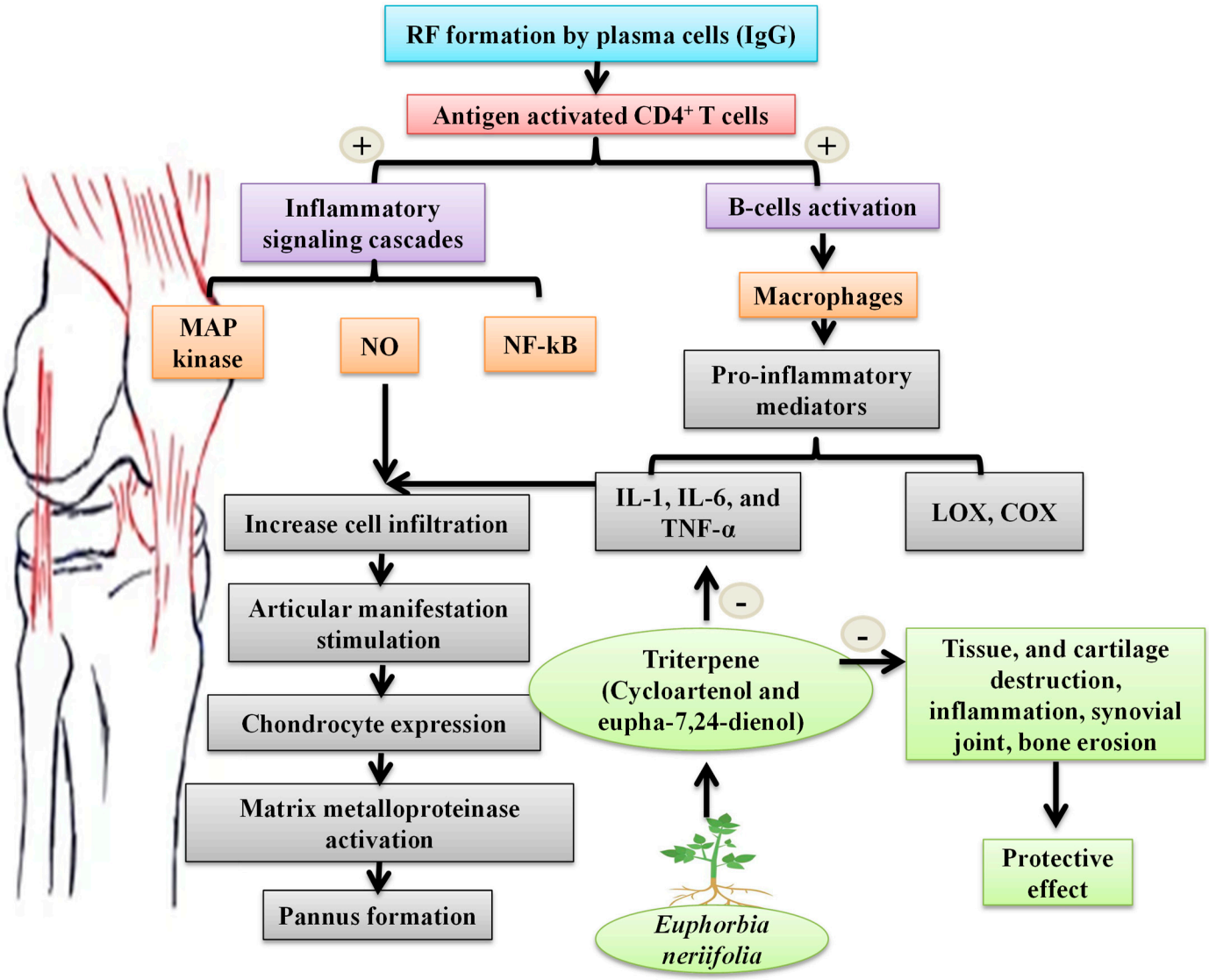


Figure 5. Anti−arthritic mechanism of medicinal plant. (MAPK: mitogen activated protein kinase; NO: nitric oxide; NF-kB: nuclear factor kappa B; IL-1: interleukin 1; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; LOX: lipooxygenase; COX: cyclooxygenase).

In determining the anti-inflammatory activity, the hydroethanolic extract of medicinal plant causes a reduction in the levels of prostaglandin E-2 and nitric oxide by not affecting the cyclooxygenases-2 but by affecting the nitric oxide synthase in LPS-directed RAW 264.7 murine macrophages [116]. A further reduction in the interleukin (IL)-1β and tumor necrosis factor levels was observed with elevated levels of interleukin IL-10. Modulation in the early and late phase mediators may be responsible for the anti-inflammatory activity of a plant. In the Unani medicinal system, *E. neriifolia* is utilized to treat inflammation either solely or in combination with some other drug [117]. Six euphanes and seven undescribed triterpenes such as neritriterpenoidal C, neritriterpenols A–B and D–G, along with four known triterpenes were isolated from the ethanolic fraction of the *E. neriifolia* stem. Structural activity relationship (SAR) studies determined that the presence of an unsaturated group at the end of the side chain C17 on euphane-type triterpenes may be related to the anti-proliferative and anti-inflammatory activities of these compounds [12].

12.5. Anti-Arthritic Effect

Rheumatoid arthritis (RA) is an autoimmune disorder that is determined by various deformities such as systemic complications, peripheral neuropathy amyloidosis, pulmonary fibrosis, pericarditis, and vasculitis. The main feature of RA is symmetric polyarthritis that directs pain in muscles, and it is identified by the help of biomarkers such as elevated levels of IgA and IgM [118]. Various genetic and environmental factors contribute to this disease by immune cell activation, such as synovial fibroblasts, macrophages, and monocytes that further initiate antigen-activated $CD4^+$ T cells. The activation of $CD4^+$ T cells leads to the production of cytokines such as TNF-α, IL-6, and IL-1 as the main mediators. These pro-inflammatory mediators are involved in the pathogenesis of RA, such as an increase in the inflammatory infiltration of cells, namely, B cells, T cells, and macrophages, and bone erosion due to the release of IL-6 and TNF-α, as well as the production of autoantibodies. These cytokines further obstruct the synthesis and degradation of collagen and proteoglycan. The cartilage damage is triggered in response to activated proteolytic enzymes such as collagenases and MMPs [119].

Furthermore, cytokines and chemokines result in synovitis and the destruction of tissue by attracting cyclooxygenase (COX)-2 enzymes, neutrophils, monocytes, and lymphocytes, which trigger hyperplasia and the formation of pannus in the synovial joints. All these happenings cause further apoptosis in synovial fibroblasts. The treatment of arthritis with synthetic drugs majorly targets the inflammatory mediators to decrease the inflammation and to prevent the deterioration of the joint. Currently, the application of traditional plants and herbs as conventional therapy has gained the interest of researchers in the exploration of new drugs due to higher compatibility and fewer side effects with long-term usage compared to synthetic ones [120].

The modulation of IL-1β, IL-6, and TNF-α occurred in response to terpenes against arthritis. Several pieces of research reported that the blockage of TNF-α resulted in a clinical benefit in various inflammatory diseases. Antagonization of the IL-6 receptor has also resulted in clinical improvement in rheumatoid arthritis patients. In some studies, terpenes caused modulations in various intercellular signaling pathway proteins, such as c-FOS, MPO, matrix metalloproteinases, PGE-2, iNOS, COX-2, MAPK family, NF-kB, and RANKL, due to their beneficial pharmacological properties against arthritis (Figure 5). The inhibition and activation of these pathways or molecules in response to terpenes can reduce the propagation of disease [121].

Similarly, the triterpenoidal-rich leaf fraction of *E. neriifolia* showed the presence of cycloartenol and eupha-7,24-dienol. Pre-treatment with this fraction significantly reduced the cytokine TNFα, arthritis index, and paw edema in a CFA-induced arthritic model after treatment for 28 days. Thus, maintenance of the functional ability of the synovia and the decrease in inflammatory process may be due to the inhibition of leukotriene infiltration and cytokines, which was determined by a decrease in the arthritic index and TNFα, respectively [112].

12.6. Wound Healing Property

Wound healing is a natural but complex and systematic process that includes three phases, including the maturation phase, proliferative phase, and inflammatory phase [122]. Medicinal plants or their phytocompounds are used traditionally to treat wounds. Many of the phytocompounds have been utilized for the discovery of new inputs in the pharmaceutical industry. These compounds are phenolics, saponins, terpenoids, flavonoids, essential oil, and alkaloids. Various studies reported the effect and activities of herbal drugs with antioxidant and anti-microbial properties that accelerate the healing of a wound and skin regeneration [123].

Normal healing includes: Epidermis—there is a release of blood components at the injury site due to the inflammation of the epithelial cells. The components of blood are mast cells, macrophages, neutrophils, platelets, growth factors, and cytokines. The neutrophils generate free radicals at the injury site that result in a respiratory burst. Platelets release

essential growth factors such as transforming growth factor (TGF-β) and platelet-derived growth factors (PDGF) and cytokines. These growth factors further activate macrophages and directly release interleukin-1 (IL-1), fibroblast growth factors (FGF), and tumor necrosis factor-alpha (TNF-α) at the wound site [99]. Dermis—activates releasing factors and recruits resident fibroblasts, which differentiate into smooth muscles and myofibroblasts, resulting in connective tissue deposition and wound healing. Endodermis—wound healing is accomplished by fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) in the blood vessels, which are recycled and activate additional activation of resident fibroblasts ([124] Figure 6).

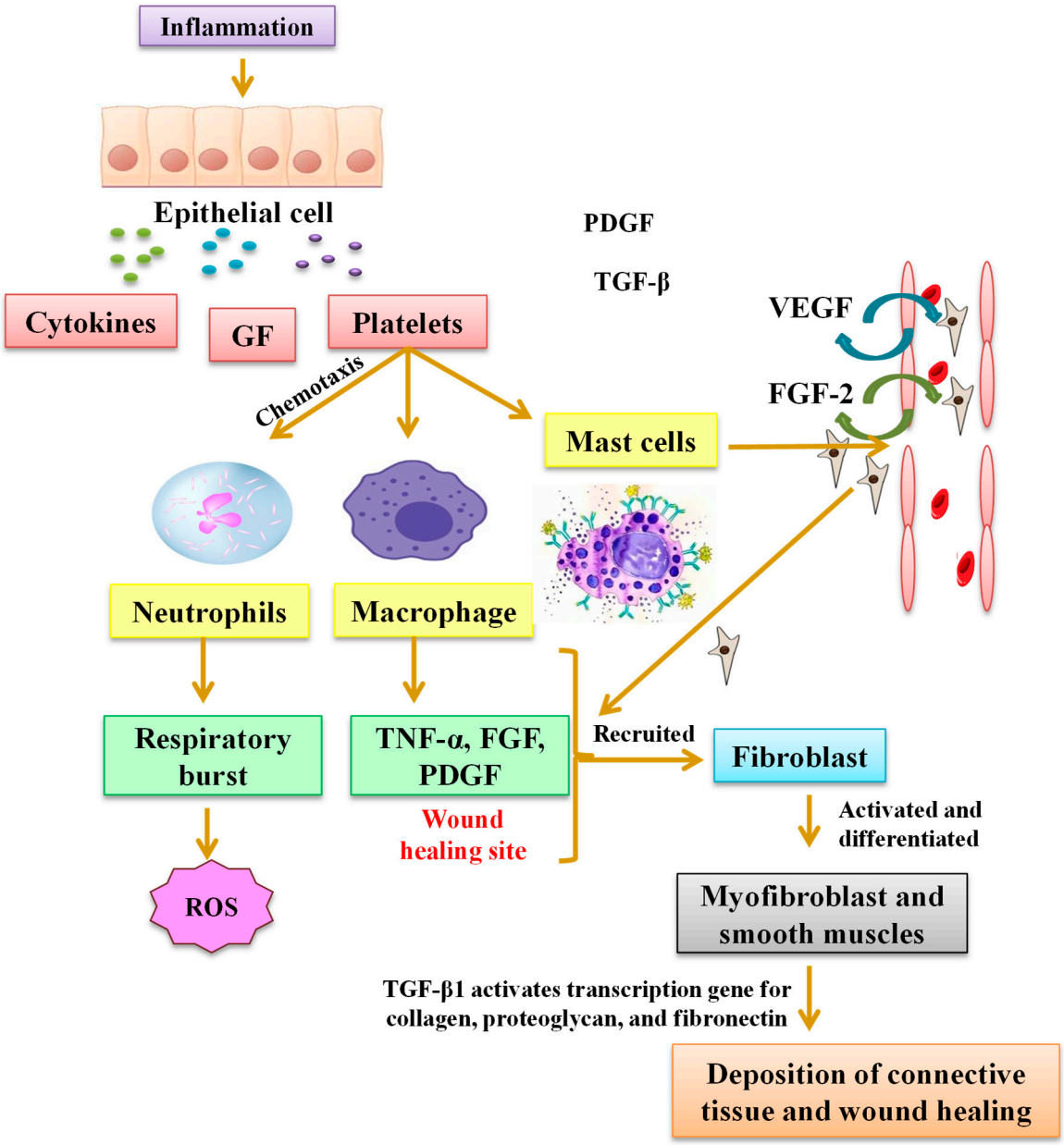


Figure 6. Mechanism of normal wound healing. (VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor; PDGF: platelet derived growth factor; TGF-β: transforming growth factor-beta; TNF-α: tumor necrosis factor alpha; GF: growth factor).

Plant extract directed wound healing: Over expression of TGF-β1 results in premature human fibroblast senescence. VEGF is activated by the treatment with plant extracts, which causes a signal to keratinocytes to increase the angiogenesis at the wound site. The VEGF

further activates extracellular matrix glycoprotein to heal the wound; and it also directs the dermal fibroblast proliferation that results in the production of adhesive molecules, cytokines, glycoproteins, ECM, and the formation of a fibroblast–keratinocyte–endothelium complex. Enhanced differentiation and plasticity of human adipose-derived stem cells, including myocytes, adipocytes, osteocytes, and chondrocytes, and alkaline phosphatase activities increase the collagen synthesis at the wound site, as shown in Figure 7 [125].

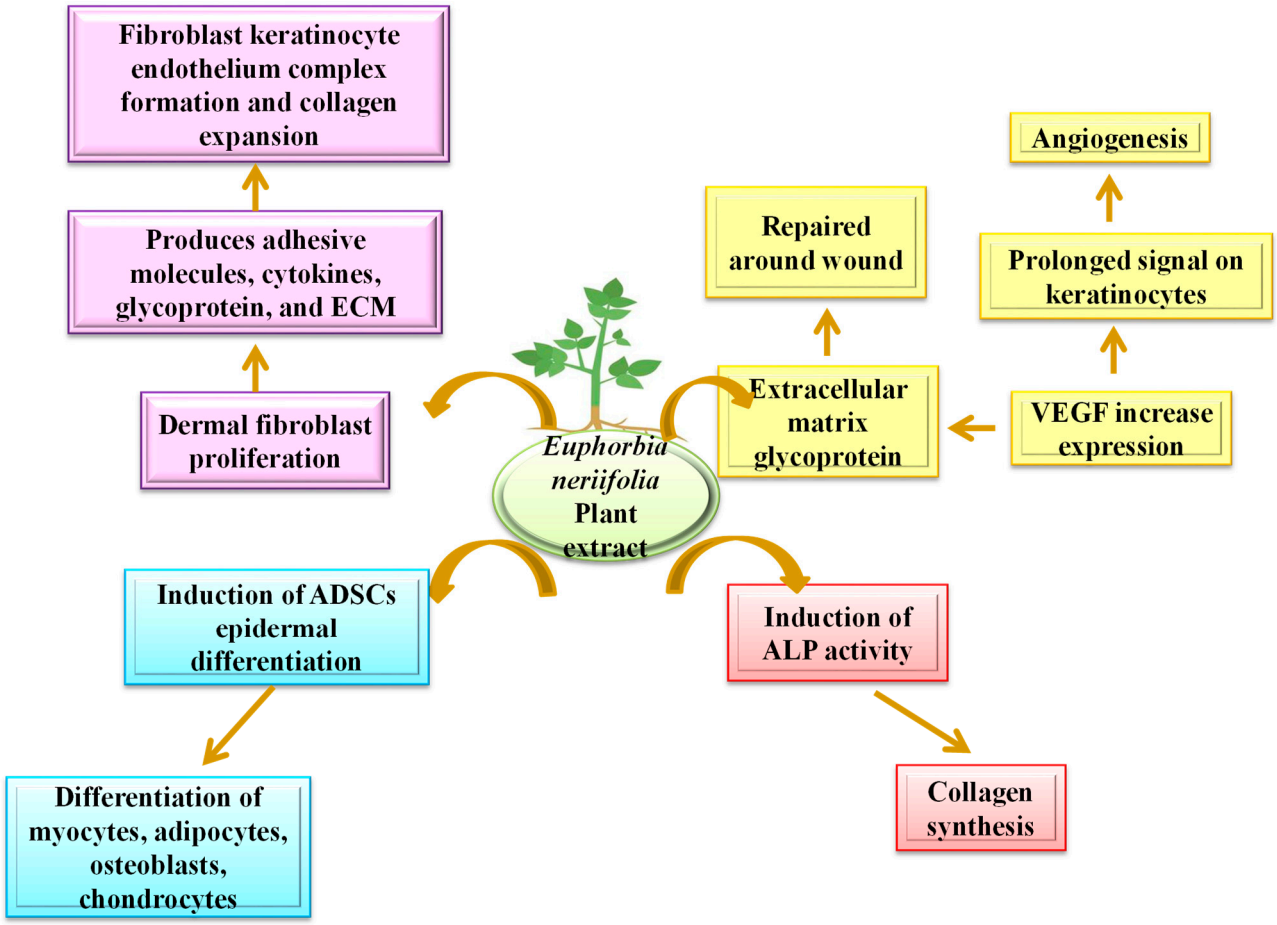


Figure 7. Role of plant extract in inducing wound healing. (ECM: extracellular matrix; ALP: alkaline phosphatase; ADSCs: adipose derived stem cells; VEGF: vascular endothelial growth factor).

12.7. Anti-Artherosclerosis Activity

Cardiovascular diseases (CVDs) are one of the main health issues that account for 30% of mortality across the globe. These CVDs primarily include inflammatory heart diseases, cardiac dysrhythmias, deep vein thrombosis, peripheral arterial disease, cerebrovascular disease cardiomyopathy, and coronary heart disease (CHD). The CVD etiology is very complex but hypertension and atherosclerosis are the two common factors which are responsible for CVDs [126]. Atherosclerosis is a multifactorial chronic disease that is determined by inflammation and dyslipidemia. It is one of the reasons that the cause of mortality due to cardiovascular diseases in developed countries has increased. It develops in the arteries of humans for many years and remains undetected for a long period of time [127].

Environmental factors (lack of exercise, infectious agents, high-fat diet, smoking, etc.) and genetic components (obesity, insulin resistance, hypertension, etc.) are some major risk factors that cause atherosclerosis. The pathophysiology of atherosclerosis includes: hyperlipidemia, which causes an increase in the uptake of LDL in the endothelial cells where these cells undergo some minimal changes and become modified LDL. Further

oxidants act upon the modified LDL and lead to the formation of oxi-LDL. Conversely, the dysfunction of endothelial cells leads to the adhesion of monocytes (triggered by the modified LDL) to the cell surface, and they enter inside the endothelial cells and further differentiate to form macrophages. These macrophages uptakes the oxLDL through the receptor CD-36 and SR-A by pinocytosis and phagocytosis. The intracellular cholesterol esterifies via imbalanced levels of nCEH and ACAT1. Then the esterified cholesterol releases through ABCA1 and ABCG1, which leads to the formation of foam cells. These cells are responsible for the inflammatory process, which results in the migration of smooth muscle cells and the formation of plaques. Finally, the plaque is ruptured, which results in the blockage of arteries and, therefore, decreased blood flow, as shown in Figure 8 [128].

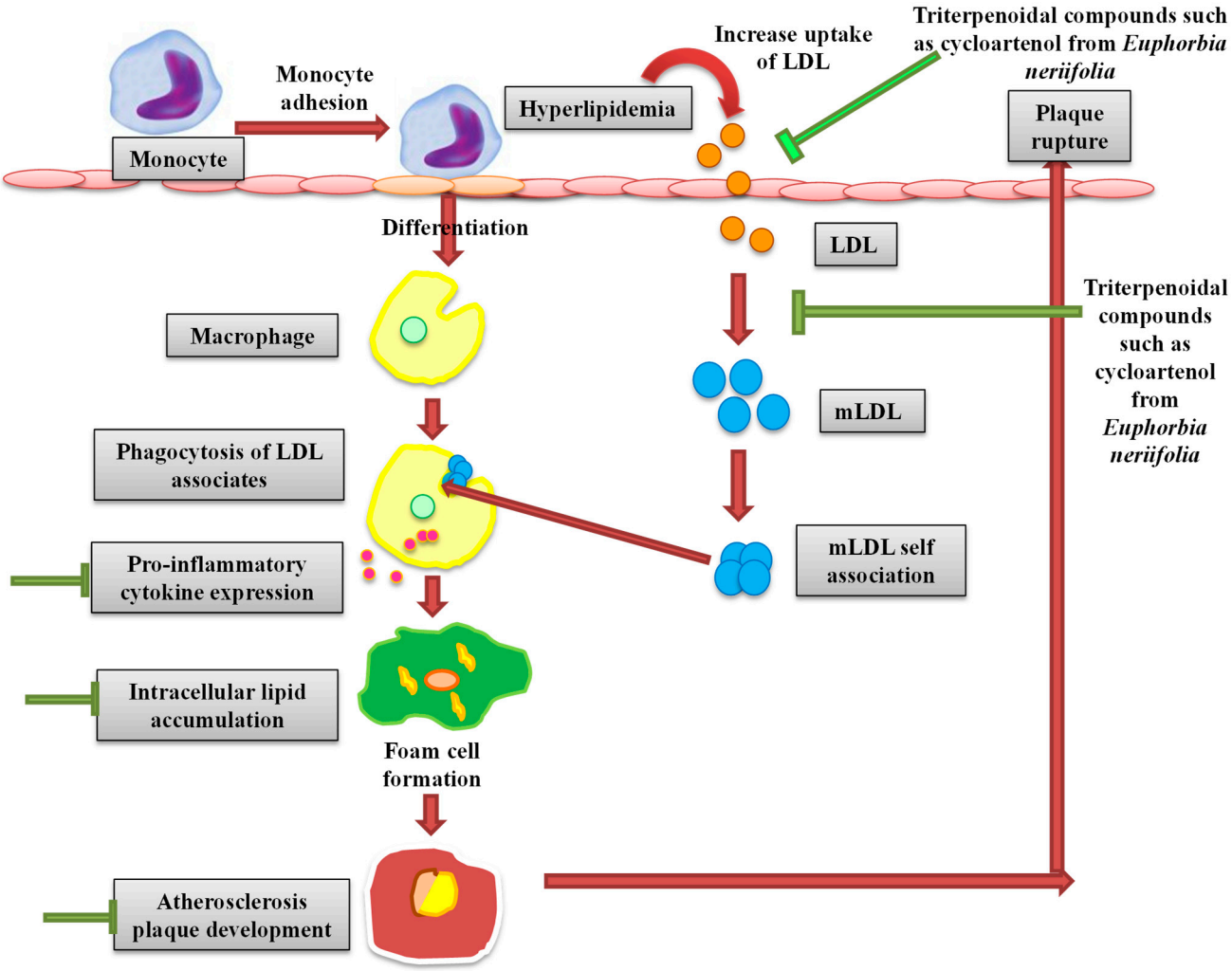


Figure 8. Pathophysiology of atherosclerosis. (LDL: low density lipoprotein; mLDL: modified low density protein).

Various studies described the role of pro-inflammatory cytokines in the formation of atherosclerosis lesions in the wall of arteries. The results obtained from several studies explained the need to use anti-cytokine therapy to deal with the changes at early stages of atherosclerosis formation. Currently, it was evaluated that the phytocompounds, such as triterpenoids from the medicinal plant *E. neriifolia*, were capable of modulating the pathways related to inflammation by restricting the uptake and modification of LDL. Many of these natural compounds have no side effects and can be utilized for the long-term treatment of atherosclerosis [127].

12.8. Radio-Protective Property

Humans are exposed to higher levels of ionizing radiation, which cause an increase in the production of free radicals within the body. These free radicals induce damage to lipid, protein, DNA, and cellular structures that results in the dysfunction of the immune and hematopoietic systems, promotes degenerative pathological changes, and accelerates the process of aging [129].

Different forms of ionizing radiation exist naturally, including neutron, gamma, beta, alpha, and X-rays. Radioactive isotopes emit alpha radiation, which consists of alpha particles, whereas radioactive nuclei release beta radiation, which contains negatively charged high-energy electrons. The penetration power of beta radiation is high compared to alpha radiation. Gamma radiation is an electromagnetic radiation similar to ultraviolet (UV) light, radio waves, and visible light. Ionizing radiation causes a series of biochemical alterations that consequently lead to necrosis, injury, and other harmful effects. According to some studies, the damage caused by ionizing radiation to the human body can occur through indirect and direct methods. Direct damage occurs when biological macromolecules come into physical contact with ionizing radiation, which results to injury. The indirect damage includes free radicals that are formed from the molecules of water inside the irradiated body. Exposure to radiation stimulates the production of strong oxidizing molecules such as NO, H_2O_2, O^{2-}, and OH^-. These free radicals react with the macromolecules that significantly change the function and structure of biological macromolecules, resulting in the occurrence of fatal diseases [130]. The deteriorating effects of radiation generate a requirement for radioprotectors to avoid the degree of lethality linked with radiation or to safeguard the all-important organs of our body [131].

Plants have a naturally gifted ability to control the harmful effects of radiation coming from the sun. Therefore, it is determined that the plants are equipped with various defense machineries that provide protection to themselves against the radiation-stimulated oxidative stress and injuries. The application of phytochemicals as radioprotectors has gained much attention that has resulted in the discovery of certain agents with special antioxidant properties. These phytocompounds are quite popular due to fewer harmful effects, good radioprotection ability, lower cost, and easy availability. Several mechanisms, such as anti-lipid peroxidation potential, improvement in the status of antioxidants, and free radical scavenging activity, were employed to provide protection against radioactivity. This protection is possible due to the presence of different phenolic hydroxyl groups that are attached to the ring structure. Polyphenols from *E. neriifolia* such as isoflavones and their derivatives, flavonoid glycosides containing ketone groups were conjugated to aromatic rings and activated by electron donor substituents. Thus, it results in the inhibition of energy transfer, stabilization of the redox process, and suppression of the oxidative stress in the cells [132].

The polyphenolic compounds may also upregulate mRNAs of different antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase, and superoxide dismutase. This process counteracts the oxidative stress induced by radiation. The inhibition of genes such as protein kinase C (PKC), mitogen activated protein kinase (MAPK), cytochrome P-450; nitric oxide; regeneration of hematopoietic cells; maintenance of antioxidant enzyme levels and anti-inflammatory factors; and up-regulation of DNA repair genes may also provide protection against radiation-induced cellular damages. Plant extracts effectively restore the divided equilibrium, while radiation injury, in a holistic and collective manner, is due to the varied spectrum of phytochemicals, as shown in Figure 9 [133].

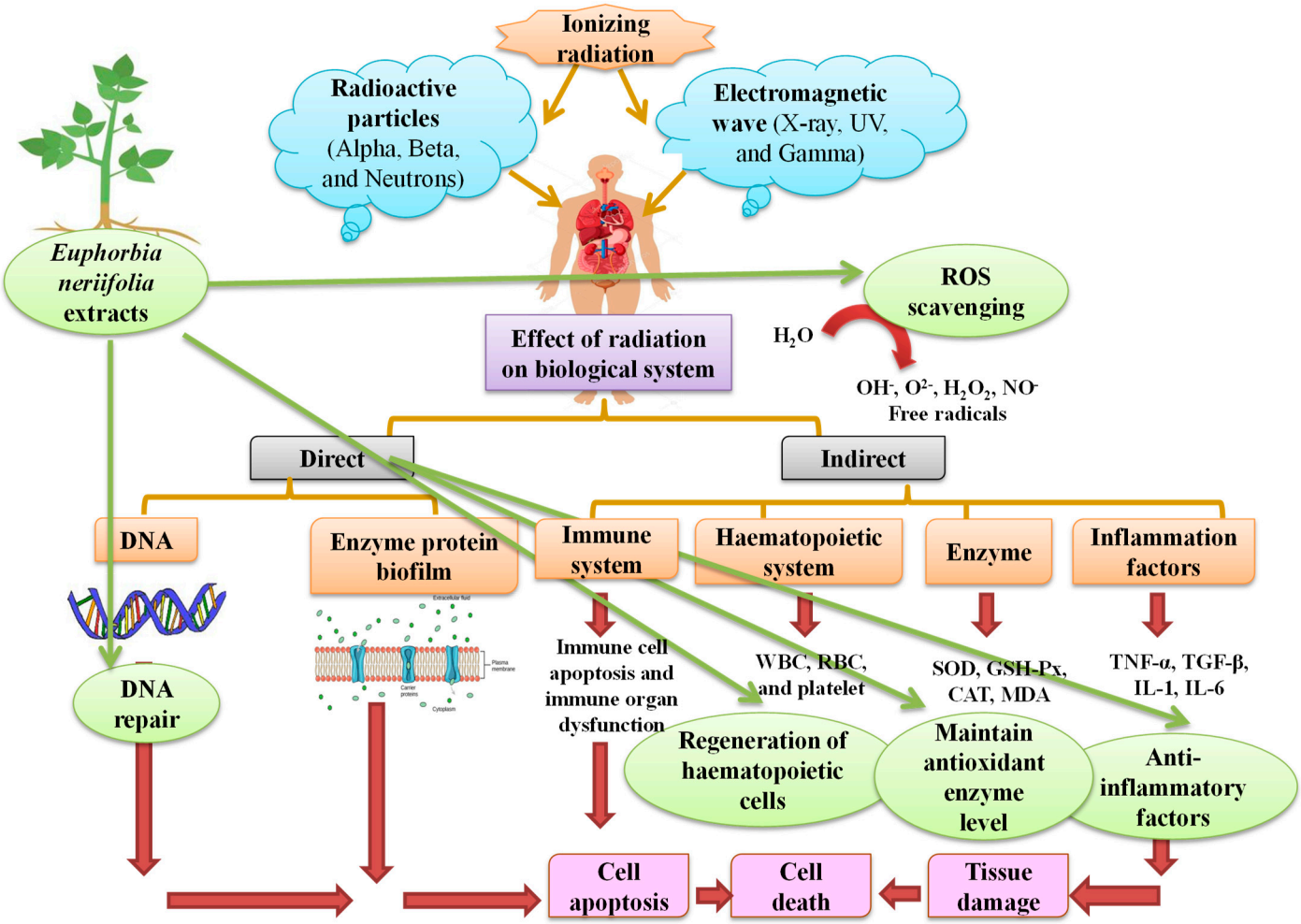


Figure 9. Radioprotective activity of medicinal plant. (WBC: white blood cell; RBC: red blood cell; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase; CAT: catalase; MDA: malondialdehyde; TNF-α: tumor necrosis factor alpha; TGF-β: transforming growth factor-beta; IL-1: interleukin-1; IL-6: interleukin-6).

12.9. Central Nervous System Diseases

12.9.1. Anti-Anxiety

Anxiety disorders are disabling conditions that are highly co-morbid and chronic. The conventional psychological interventions and pharmacotherapies are front-line approaches that involve herbal drugs as an effective and safe option. Phytocompounds that are used to treat anxiety disorder are called "anxiolytics", and they mainly affect the γ-aminobutyric caid (GABA) system either by interactions with different ranges of monoamines, the inhibition of glutamic acid or GABA transaminase decarboxylase binding with benzodiazepine receptor sites, alterations in membrane structure, or induction of the transmission of the ion channel through voltage gated blockage [134]. Hyponics and sedatives are the most extensively used drugs in the treatment of depression, insomnia, and anxiety. Long term usage of these available synthetic drugs causes life threatening diseases. Benzodiazepine and barbiturates are commonly utilized CNS depressants that interact with the postsynaptic GABAA receptor. The main drawback of these agents is physiological and psychological tolerance and dependence as well as the dysfunction of the immune system that results in the deterioration of cognitive function [135].

A limitation of anxiety drug therapy is the large number of side effects and co-morbid psychiatric disorders that have forced the scientists to investigate plants for sleep disorders and other related diseases. Alternative and complementary therapies are utilized more

frequently than the conventional ones by people with severe depression and anxiety attacks. The application of these therapies had a promising effect by maximizing the usefulness of therapy and the prevention of side effects [136].

12.9.2. Anti-Convulsant

Convulsions are the result of rapid and excessive discharges in the grey matter of the brain. Convulsions have a focal origin, which means the type of seizure depends upon the focus site in the brain, the region where discharge spreads, which affects the postictal paralysis of these regions. Anti-convulsants are utilized to inhibit discharge and, consequently, the hypnosis. The drugs show their effect either by modifying the brain neurotransmitter or by changing the membrane permeability to all ions. An increase in GABA concentration and alterations in the glycine and serotonin concentration was observed during the action of these drugs [137].

12.9.3. Anti-Psychotic

Various synthetic and psychoactive compounds such as anxiolytics, anti-depressants, and neuroleptics are utilized in modern medicinal system to treat these disorders, mainly psychiatric disorders, schizophrenia, and epilepsy. However, these treatments are inaccessible, complex, and expensive for large parts of the human population [138]. The serious and main adverse effects of these drugs involve extrapyramidal side effects and hypotension. The impact of side effects is so high that the prescription of particular drug needs to be discontinued after a few years of utilization due to extra pyramidal side effects such as tardive dyskinesia, acute muscle dystonia, and akathisia. The requirement for drugs with fewer side effects, especially when they are administered for a prolonged period of time, is rising incredibly for the treatment of psychiatric disorders. Plant-derived drugs are known to have significantly fewer side effects, so it is well worth utilizing them for the therapy of chronic CNS diseases [139].

Several efforts were made to isolate phytocompounds from specific plant fractions that were determined to have CNS activity [140]. The hydro-alcoholic leaf extract of *E. neriifolia* was evaluated for psychopharmacological activity. There was a significant reduction in the apomorphine-induced stereotype at different doses (100, 200, and 400 mg/kg body weight) in rats and mice and an absence of cataleptic effect that suggested the modulating activity of specific dopaminergic receptors. In response to *E. neriifolia* extract, pentobarbitone-induced hypnosis and anxiolytic action were performed at 400 mg/kg dosage by raising the time spent in an elevated plus-maze. Thus, anti-convulsant activity was observed against electric-shock-induced convulsions at 400 mg/kg of dosage. The extract of *E. neriifolia* was not able to reverse the scopolamine-induced amnesia but it raised the latency at 400 and 200 mg/kg of dosage in combination with scopolamine. Thus, it was determined that *E. neriifolia* exhibits anti-convulsant, anti-psychotic, and anti-anxiety activity in rats and mice [141].

12.10. Anti-Thrombotic Property

According to current reports, cardiovascular disorders along with thrombosis are a major cause of mortality across the globe. The emergence of thrombus in a vein and artery is attributed to the aggregation and adhesion of platelets, exogenous and endogenous coagulation system, blood vessel injury, and the yield of fibrin. Thrombosis is a multifactorial complicated pathogenic process that results in the onset of various diseases including sudden death, plaques, atherosclerosis, ischemic myocardial infarction, and deep vein thrombosis. The intravascular thrombosis is one of the major factors responsible for cardiovascular diseases and approximately 99% of infarctions are caused by thrombotic or embolic events [142]. Synthetic anti-thrombotic drugs such as clopidogrel, warfarin, streptokinase, and aspirin show some side effects and might explain the vascular relapse. Palpitation, gastrointestinal bleeding, prolonged bleeding time, internal bleeding, and headache are some of the frequently occurring adverse effects. Due to this reason, it is

the need of the hour to investigate novel phytocompounds with precise and effective mechanisms of action and less toxicity [143].

Thrombosis includes the formation of a solid mass within the circulation due to the accumulation of constituents present in blood flow. The mass that forms is named a "thrombus". Blood clots and hemostatic plugs formed in healthy individuals during bleeding help with prevention of blood loss. However, the formation of thrombi in an unruptured blood vessel is quite fatal. A reduction in blood flow, the triggering of the coagulation system, and changes in the vascular endothelium are the three main factors that lead to the formation of a thrombus. The composition of a thrombus includes red blood corpuscles, platelets, and fibrin. Arterial thrombi are the result of endothelial injury that results in hasty blood flow whereas a venous thrombus is the result of a blockade of blood in the veins. Anti-thrombotic therapy involves the application of anti-coagulants, fibrinolytic agents, and anti-platelet agents. These drugs are found to be effective to treat thrombi with some side effects that need to be considered [144].

12.11. Dermal Irritation

The human skin is very sensitive to a large number of chemicals. Thus, all new formulations must be tested on skin to determine any type of irritation and erythema for a specific period of time [145]. Different extracts (acetone, petroleum ether, water, and chloroform) of *E. neriifolia* latex were determined to evaluate the dermal irritation activity in rabbits. The petroleum ether fraction was reported to be safe with a primary index score of 0.43/0.11 for erythema and edema, compared to other fractions that resulted in irritation of the skin due to the presence of diterpenes esters. The petroleum ether extract of *E. neriifolia* latex inhibited the paw edema (35.25% and 42.40%), which was the result of the carrageenan at the concentrations of 500 and 700 mg/mL [35].

12.12. Haemolytic Activity

Various compounds of *E. neriifolia* are reported to have hemolytic activity at varied concentrations, such as silymarin at 100 µg/mL of concentration, triton at 100 g/mL of concentration, and saponin at 300 µg/mL [141].

12.13. Death Receptor Expression Enhancing Activity

A novel ingol diterpene, 3-O-acetyl-8-O-tigloylingol (8), euphonerins A–G (1–7), and seven new cycloartane triterpenes were isolated from the methanolic fraction of *E. neriifolia* leaves, along with three known flavonols (11–13), (24R)-cycloartane-3β, 24, 25-triol (10), and 3,12-di-O-acetyl-8-O-tigloylingol (9). The structure of 1–8 compounds was created with the help of spectroscopic analysis. Among all compounds, 1–11 compounds have shown death receptor expression enhancing activity [88].

12.14. Analgesic Activity

Pain is an emotional experience and an unpleasant memory associated with potential damage of tissue. The most commonly used drugs for pain are morphine and aspirin. These analgesic drugs, specifically nonsteroidal anti-inflammatory and opioid drugs can relieve only 50% of pain in 30% of patients. These drugs are also associated with some side effects that determine the need to discover new agents to treat pain [146–148]. Overall, the results showed that the hydro-ethanolic extract of *E. neriifolia* has great analgesic activity. This extract has also shown significant analgesic activity at a concentration of 400 mg/kg in comparison to diclofenac sodium, as reported by Mali and Panchal [9]. The hydro-ethanolic extract inhibited the pain threshold after 60 min at a percentage of 432.22%, whereas acetic acid extract inhibited the pain at the same time and dosage at a percentage of 53.83%, respectively [9].

12.15. Anti-Diuretic Activity

Pracheta et al. [149] evaluated the anti-diuretic activity of the hydroethanolic extract of *E. neriifolia* leaves. The result, indicated by an increase in urine volume of up to 3 times (17.45 mL) in response to the extract at 400 mg/kg dosage, indicated it was an effective hypernatremic and hyperchloremic diuretic compared to control with 6.65 mL urine in the rat model.

12.16. Anti-Ulcer Activity

The ulcer is one of the gastrointestinal problems that is common in various individuals. It is an inflamed break in the mucus membrane or skin that lines the alimentary tract. This occurs due to an imbalance resulting diminished mucosal resistance and enhanced aggression due to the usage of some drugs, stress, irregular food habits, etc. Peptic ulcers are the ulcers present in the duodenum and digestive tract of the stomach. The peptic ulcer formation is based on peptic activity in gastric juice and the presence of acid along with the breakdown of the mucosal defense. Various synthetic drugs are available to treat ulcers but these may have more side effects compared to herbal drugs [150].

12.17. Anesthetic Activity

The aqueous and alcoholic extract of the *E. neriifolia* stem showed the anesthetic activity in the case of an intradermal wheal in guinea pig and in the case of foot-withdrawal in frog. The alcoholic extract was found to possess good anesthetic activity in comparison to the aqueous extract [151].

12.18. Anti-Bacterial and Anti-Fungal Activity

Various infectious diseases, particularly those targeting the mucosa and skin, are more common among the population as a result of a lack of knowledge of sanitary dietary practices, access to clean water, and adequate sanitation. The most common bacterial species in soft and skin tissue include *Staphylococcus aureus*, *Streptococcus pyogenes*, *Clostridium perfringes*, and members of the Bacteroides family of bacteria. *Pseudomonas aeruginosa*, *Pasturella tulurensis*, *Bacillus antracis*, *Neisseria gonorrhea*, *Mycobacterium tuberculosis*, and *Mycobacterium leprae* are some other bacteria reported in the environment (Table 8). Skin infections mostly occur due to fungal species such as *Trychophyton tonsurans*, *Melassezia furfur*, *Epidermo-phyton flocossum*, *Candida neoformans*, *Candida albicans,* etc. [152].

Cutaneous abscesses caused by local bacterial infections are characterized by a pus/fluid accumulation within the dermis, which is further associated with inflammation that results in skin lesions as an open sore. Severe cases of abscesses that show the signs of septic infection are not only drained surgically but may be further treated with antibiotics to prevent recurrence and dissemination. Cutaneous abscesses can be caused by various Gram-positive and Gram-negative bacteria but methicillin resistant *Staphylococcus aureus* (MRSA) is an example of bacteria that is often responsible for causing abscesses. Cutaneous abscess infections cannot be treated easily with the available therapies, and complementary alternatives are needed to treat this disease [153].

The methanolic extract of *E. neriifolia* showed anti-microbial activity against *Aspergillus niger* at different concentrations. In the case of the extract, no activity was observed at 50 mg/mL, a 2 mm zone of inhibition was observed at 100 mg/mL, and a 6 mm zone of inhibition was observed at 200 mg/mL, as well as a 12 mm zone of inhibition at 400 mg/mL, whereas an 18 mm zone of inhibition was reported in response to the control, amphotericin B. In the case of *Candida albicans*, the methanolic extract of *E. neriifolia* showed no activity at 50 mg/mL, a 4 mm zone of inhibition at 100 mg/mL, a 10 mm zone of inhibition at 200 mg/mL, and a 14 mm zone of inhibition at 400 mg/mL, in comparison to a 21 mm zone of inhibition with amphotericin B [154].

The leaves of *E. neriifolia* were subjected to heating and the juice was dried and evaluated against *Pseudomonas salanacerum*, *Staphylococcus aureus*, and *Escherichia coli*. It was determined that the dried juice of *E. neriifolia* leaves exhibit great anti-microbial activity

against these strains [155]. The reduction in gold salt with the stem of *E. neriifolia* resulted in the formation of gold nanoparticles (Au-NPs). The gold nanoparticles were of spherical shape and of 23–25 nm in size and exhibited better anti-fungal and anti-bacterial activity compared to the *E. neriifolia* stem extract [156]

Table 8. List of anti-microbial activity of *Euphorbia neriifolia*.

S.No.	Plant Part	Plant Extract	Organisms Name	Features	Diseases	References
1.	Whole plant	Ethanol and methanol extracts	*Bacillus megaterium*	Gram-positive	Brain abscess	[157]
2.	Whole plant	Ethanol and methanol extracts	*Bacillus subtitis*	Gram-positive	Food poisoning, opportunistic pathogen	
3.	Leaf	Ethyl acetate and water extract	*Pseudomonas fluroscens*	Gram-negative	Bacteremia	[147]
4.	Leaf	Ethyl acetate and water extract	*Aspergillus flavus*	Saprotrophic fungus	Allergic reactions	[68]
6.	Leaves	Ethanol extract	*Escherichia coli* and *Escherichia coli* (ATCC 10536)	Gram-negative	Gastroenteritis, urinary tract disease.	[154]
8.	Leaf	Chloroform extract	*Pemphigus vulgaris*	Gram-negative	Urinary tract infections	[158]
9.	Whole plant	Methanol and Ethanol extract	*Pseudomonas aeruginosa* and *Pseudomonas aeruginosa* (ATCC 25619)	Gram-negative	Wounds and urinary tract infections	[154]
10.	Whole plant	Methanol and Ethanol extract	*Pseudomonas putida*	Gram-negative	Skin and soft tissue infection	[159]
11.	Leaf	Ethanol extract	*Klebsiella pneumonia*	Gram-negative	Invasive infection	[147]
12.	Leaves	Leaf juice	*Staphylococcus aureus* and *Staphylococcus aureus* (ATCC 9144)	Gram-positive	Chronic osteomyletis, Meningitis, endocarditis	[154]
13.	Stem	Methanol extract	*Aspergillus niger*	Dichotomously branching, filamentous	Allergy, asthma	[154]
14.	Latex	Latex milk with chitosan	*Aspergillus fumigates*	Monomorphic filamentous fungi	Pulmonary hemorrhage, pneumonia	[160]
15.	Stem	Methanol extract	*Candida albicans* and *Candida albicans* (MTCC 227)	Dimorphic fungi	Oral thrush, gastritis, cutaneous infection	[154]

12.19. Anti-Viral Activity

Mosquitoes are well known as a vector for various diseases that affect large numbers of the population globally. *Culex quinquefasciatus* is well known to cause filarial disease, malaria is caused by *Anopheles stephensi*, and chikungunya, yellow fever, and dengue are known to be caused by *Aedes aegypti*. To improve the human health and prevent the mosquito-borne diseases, it is very important to control them [161]. Recently, phorbol esters isolated from *Euphorbiaceae* became known for their selective and potent anti-viral activity on the Chikungunya virus replication in cell culturing. With the aim to find novel compounds with anti-CHIKV activities, variable extracts from different parts of 11 Mediterranean *Euphorbia* and 1 Mercurialis species were determined for the inhibition of CHIKV replication. All ethyl acetate fractions, especially from the latex, exhibited selective and significant anti-viral activity in a Chikungunya virus-cell-based assay [162].

Acquired immunodeficiency syndrome (AIDS) is one of the most deadly diseases worldwide. Accordingly, much effort was required for the discovery of anti-HIV-1 drugs. Emtricitabine, nevirapine, and zidovudine are some of the available drugs that have been utilized for the treatment of an HIV-1 infection. These anti-retroviral therapies are associated with drug resistance problems and many side effects. Therefore, there is a need to find new and more potent anti-HIV agents. Various phytocompounds such as diterpenes that are naturally occurring in the genus *Euphorbia* contain anti-HIV activity and could be utilized as a potential source for the development of anti-AIDS agents [57]. The coronavirus (CoV) belonging to the family Coronaviridae, is a positive strand RNA virus with the largest genome of 27–32 kb. The first study on human CoV was done in 1960, and then, a CoV was determined almost after 40 years as the causative agent of SARS, which created a global concern. A greatly effective health response from the global public prevented the spread of SARS-CoV from its endemic regions. Recently, a new HCoV has emerged that required immediate action to prevent further spread. Glycyrrhizin and interferon are some of the treatments that are available so far to treat SARS. The anti-viral activity of triterpenoidal saponin, glycyrrhizin, and their broad distribution in medicinal plants provide an interesting opportunity in the finding of novel lead drugs targeting HCoVs. Chang et al. [72] determined the anti-viral activity of one flavonoid glycoside and 22 triterpenoids from *E. neriifolia*, and it was determined that the 3β-Friedelanol exhibited better anti-viral activity in comparison to actinomycin D (control) against HCoVs. This study provides support for the addition of friedelanol-containing triterpenoids in the development of anti-HCoV agent with anti-SARS-CoV-229E molecules [72].

12.20. Anti-Venomic Property

A snake bite is a common hazard that leads to a high rate of mortality in India, and the major poisonous snakes found in India are the saw scaled viper, Russell 's viper, krait, and cobra. Anti-venom immunotherapy is the only way to treat snake venom envenomation but it exhibits various side effects such as serum sickness, pyrogen reaction, and anaphylactic shock. The World Health Organization regarded this disease as "Neglected Tropical Disease". This should be considered as a matter of health concerns for the rural and general communities of developing countries [163].

The people in some areas prevented the entry of snakes into their houses by cultivating *E. neriifolia* into their home courtyard. The extract obtained from the *E. neriifolia* root was directly applied to the stung wound site and were also administered orally in the form of drops every 3 h [164]. Approximately 64 plant species were studied against the fibroblast cell line to evaluate the antidote property of the medicinal plant against the venom. Among all, *E. neriifolia* has shown better effectiveness against the venom-treated fibroblast cell line. The venom is mainly composed of enzymes, cytotoxic agents, neurotransmitter toxins, and lipids that predominantly target the sodium and potassium ion channels. After being directly applied to the wound area, the aqueous extract of *E. neriifolia* relaxes the pain and inflammation in the bitten area [5].

12.21. Anti-Diarrheal Activity

Diarrhea is the second main cause of mortality among children below five years of age, after respiratory diseases. This disease majorly targets the individuals in developing countries and approximately 78% of child deaths were observed in South-East Asian and African countries. Diarrhea is one of the symptoms of intestinal tract problems that can result from a variety of microorganisms, such as Helminths, Protozoa, *Shigella* species, *Vibrio cholera*, *Escherichia coli*, Cytomegalovirus, Norovirus, and Rota virus [165].

The extract of *E. neriifolia* leaf increased the defecation frequency and also the number of deformed and wet feces. The purging index was increased to 286.22 in response to *E. neriifolia* extract, compared to 201.63 from the vehicle control, and resulted in an increase in wet defecation. The *E. neriifolia* leaf extract did not produce diarrhea but in combination with

castor oil, it resulted in the production of diarrhea at an increase of 20.29% in comparison to castor oil alone [35].

12.22. Anti-Asthmatic Property

Asthma is an inflammatory disease that causes the narrowing of airways and is associated with changes in the levels of cytokines, lymphocytes, mast cells, eosinophils, and other inflammatory cell products. Asthma affects approximately 300 million people worldwide with the highest number of cases in industrialized industries. Medicinal plants utilized to treat asthma may have allergic activity, smooth-muscle relaxants, anti-histamine, immunomodulatory, and anti-inflammatory activities. Currently available therapies lack the potential effect due to side effects; hence, patients are demanding alternative and complementary medicine to treat asthma [166].

The ethanol, ethyl acetate, and chloroform extracts from *E. neriifolia* were screened for their anti-asthmatic activity using milk-induced eosinophilia at 150–600 mg/kg, p.o. in mice, acetylcholine- and histamine-induced bronchospasm in guinea pig, and histamine-directed contraction on isolated guinea pig ileum and tracheal chain at a 10 mg/mL dosage. *E. neriifolia* ethanolic extract caused no toxicity at the dosage of 2000 mg/kg p.o. whereas ethyl acetate extract showed the most significant anti-asthmatic property in all models. This could be possibly due to the presence of phytocompounds such as saponins and flavonoids in the *E. neriifolia* fractions [167]

12.23. Anti-Fertility Activity

Medicinal plants are considered to be of great interest to human health. Plant-derived drugs have been a part of traditional system in different parts of the world since ancient times. Various biologically active compounds were reported from plants and many of them exhibited anti-fertility properties and thereby can be utilized for the development of antifertility drugs. Plant extracts at a concentration of 200 and 400 mg/kg resulted in no alterations in the weight of the ovaries and levels of cholesterol compared to control. There was inhibition of implants in uterine horns at both dosages of the plant extract (66.66% and 16.66%) compared to control [45,168]. The anti-fertility activity of the hydroethanolic extract of *E. neriifolia* was determined. Pretreatment with ethanolic extract resulted in the inhibition of the number of implant sites at the dosage of 400 mg/kg. No specific change in ovulation was observed; hence, this plant extract can be considered for the formation of anti-fertility drugs [45,168].

12.24. Fish Stupefying Property

In some regions of Rajasthan, the tribal peoples used the dendrons of *E. neriifolia* to catch fish, as reported by Joshi et al. [169].

12.25. Pesticidal Effect

Various dilutions of latex (0%, 25%, 50%, 75%, and 100%) were utilized against pest larvae at different time intervals (12 h, 24 h, and 48 h). The rate of mortality was determined against the three larval species at different dilutions. The selected extract of *E. neriifolia* showed effectiveness against agricultural pest species such as *Mythimna seperata*, *Helicoverpa armigera*, and *Raphidopalpa forcicollis* with a 32.99% mortality rate [5].

12.26. Anti-Cancer Properties

Cancer is a deadly disease and represents one of the major health issues for the human population that requires a proactive strategy for its treatment. The uncontrolled division of a normal cell results in genetic alterations and instabilities that accumulate within the tissues and cells and transform normal cells into abnormal ones. These instabilities include mutations in the genes of DNA repair (p53, p51, p27, p22, and p21), tumor suppressor genes (RB, NF2, NF1, and p53), oncogenes (RAS, Bcl-2, RAF, and MYC), and genes that are involved in the metabolism of cell growth. Both internal (hormonal disorders, body

immune system, and genetic mutations) and external factors (infectious agents, certain metals, chemicals, polluted air, polluted food, polluted drinking water, tobacco, smoking, and radiation) can result in cancer. There are different types of cancer reported in human beings, but among them, lung cancer is the most common in males and breast cancer in females. Different chemotherapies are available to treat cancer, but they are accompanied by a large number of side effects. However, plants and their derived products have revolutionized the field of treatment as they are less toxic, fast, low-cost, eco-friendly, safer, and simple in comparison to other treatment methods. Moreover, phytocompounds are specific in their functions and target tumor cells specifically without causing harm to normal cells, as shown in Figure 10 [170].

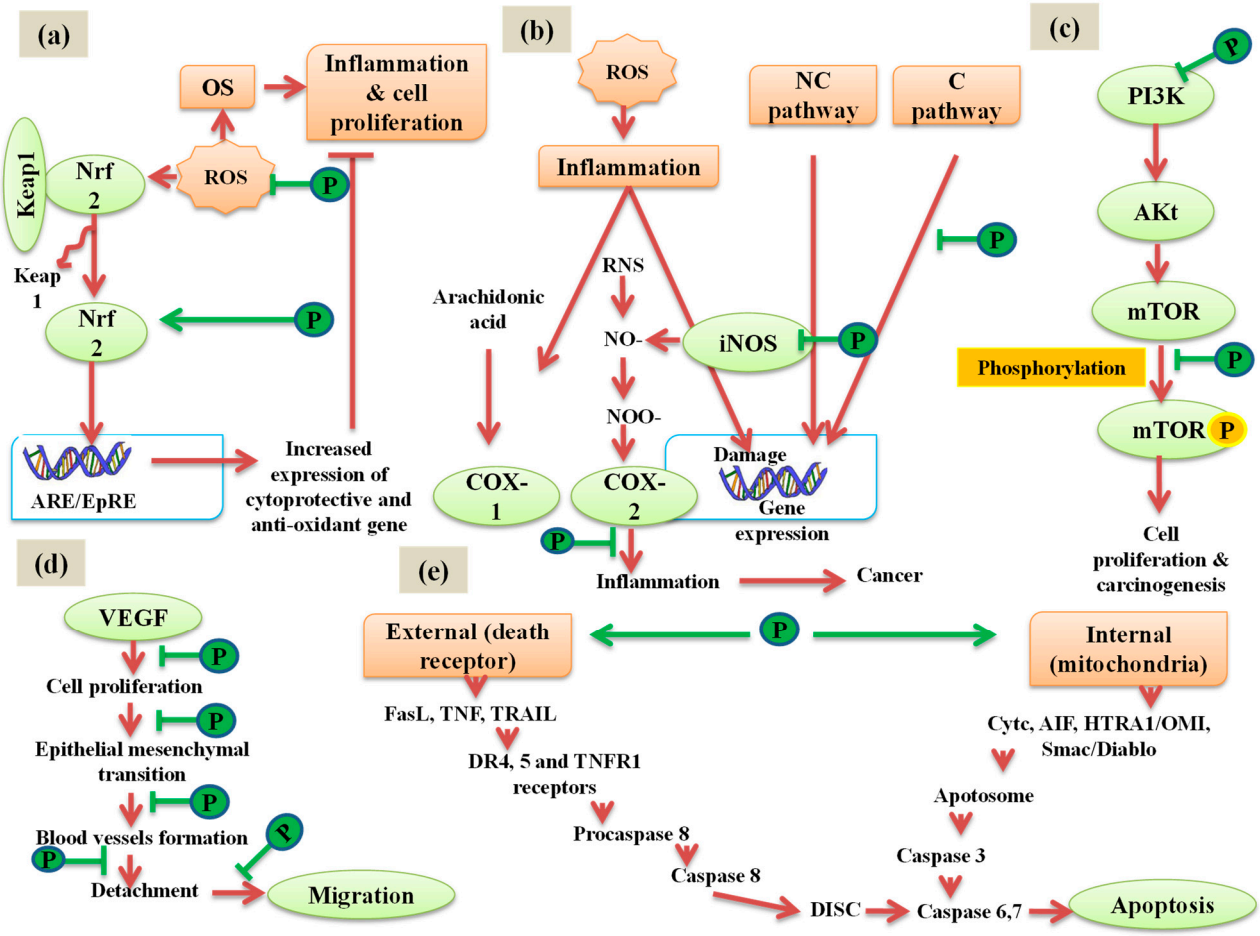


Figure 10. Anti-cancer mechanisms of phytocompounds. (**a**). oxidative stress induced inflammation and cell proliferation; (**b**). inflammation and cancer; (**c**). cell proliferation and carcinogenesis; (**d**). cell migration; (**e**). cell apoptosis. (OS: oxidative stress; ROS: reactive oxygen species; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; EpRE: electrophile response element; RNS: reactive nitrogen species; iNOS: inducible nitric oxide synthase; COX: cyclooxygenase; PI3K: phosphatidylinositol-3 kinase; mTOR: mammalian target of rapamycin; VEGF: vascular endothelial growth factor; FasL: Fas ligand; TNF: tumor necrosis factor; TRAIL: TNF-related apoptosis-inducing ligand; DR4: death receptor 4; TNFR1: tumor necrosis factor receptor 1; Cytc: cytochrom C; AIF: apoptosis inducing factor; HTRA1: high temperature requirement A serine peptidase 1; Smac: second mitochondria derived activator of caspase; Diablo: direct inhibitor of apoptosis binding protein with Low pl).

12.27. Cytotoxicity

A triterpenoid cycloartenol is being utilized to treat human cancer cell lines, as reported by Smith-Kielland et al. [171]. Other triterpenoids, such as 3-b-friedelinol, 3-a-friedelinol, and 3-β-taraxerol from *E. neriifolia,* have shown inhibitory activity against 81T, Panc-1, and BE3 cancer cell lines with a 60% inhibition rate at 10 µm concentration, whereas 3,12-o-diacetyl-7-o-angeloyl-8-methoxyingol, 3,7,12-o-triacetyl-8-o-tigloylingol, and 3 beta-friedelinol have shown cytotoxicity in the K562 cell line with 53%, 42%, and 45% inhibition at 10 µm concentration. Triterpenoidal compounds were more cytotoxic to the BE2, 81T, and Panc-1 cell lines, whereas lingols were cytotoxic to the K562 cell line [26].

Radiation-induced alterations in the cultured human lymphocyte model showed inhibition in the growth of mouse melanoma cells by 50% (173.78 µg/mL) in comparison to standard vincristine (120 µg/mL) [172]. Moreover, diterpenoids from *E. neriifolia,* such as ingenol 3,20-dibanzoate, and phorbol 12-tiglate 13-decanoate, were found to be effective for the treatment of lymphocytic leukemia (P-388) in case of mice [173]. Thus, the extracts and isolated compounds of *E. neriifolia* can be further studied for in vivo studies.

12.28. Renal-Protective Activity

The third most common malignancy across the world is kidney cancer, which accounts for 1–2% of all cancers in women and 2–3% in men with 63,000 deaths and 130,000 new cases annually. Some toxic medicines, chemicals, and substances are responsible for inducing kidney cancer [174]. Among nitrosamines, N-Nitrosodiethylamine (DENA) is one of the environmental carcinogens that is considered a human carcinogen on the basis of its carcinogenicity in an experimental animal model. DENA caused cellular injury and oxidative stress due to the generation of free radicals. This carcinogen is commonly reported in vegetables such as soybeans, soft drinks, alcoholic beverages, meat and milk products, and drinking water. The peroxidation of lipids and other membrane-associated damages are some key features of DENA-induced carcinogenesis. The effectiveness of synthetic drugs is well-determined; however, they are linked with some side effects and one of them is carcinogenicity. Thus, there is a need to find naturally derived antioxidant molecules that are less toxic and have better scavenging properties than the synthetic ones.

The administration of DENA (50 mg/kg) significantly reduces the levels of GSH, GST, CAT, and SOD with increased levels of LPO, Cyt b5, Cyt P450, along with an increase in tissue weight and decrease in body weight. The renal markers and activities of TP, ALP, ALT, and AST were also reduced with the increase in TC level. Pretreatment of ENF at the concentration of 50 mg/kg and *E. neriifolia* at the concentrations of 150 and 400 mg/kg showed positive effects by restoring the levels of xenobiotic enzymes (Cyt b5 and Cyt P450), renal markers (creatinine and urea), biochemical parameters (TC, TP, ALP, ALT, and AST), and antioxidants (GSH, GST, CAT, and SOD) in the case of the tissues. Thus, the hydro-ethanolic extract of *Euphorbia* and its isolated flavonoid has shown significant anti-carcinogenic activity against DENA-induced renal cancer [175].

12.29. Hepatoprotective Activity

Hepatocarcinoma is a major problem in both developed and developing countries. It is considered to be the fifth most deadliest cancer, which accounts for 83% of all cases with poor diagnosis. It is determined to be induced by fungal toxins, food additives, air pollutants, and toxic industrial chemicals. Different types of chemotherapeutic agents have been utilized to treat cancer, such as paclitaxel, 5-fluorouracil, and cisplatin. However, these synthetic drugs have certain problems due to multidrug resistance and a low number of apoptotic proteins [176].

Liver carcinogenicity was induced after the administration of DENA at 50 mg/kg body weight of concentration in male albino mice. Exposure of DENA caused alterations in the normal histo-architecture that comprised vacuolization of the cells, dilated sinusoids, and necrosis with decreased levels of endogenous antioxidant enzymes (CAT and SOD) and increased LPO activity. Pretreatment with the hydroethanolic extract of *E. neriifolia* and

its isolated flavonoid significantly restored the levels of antioxidant enzymes in the liver. Thus, the ethno-medicinal use of the *E. neriifolia* was proven to cure liver cancer [62,142]. The methanolic extract of *E. neriifolia* was evaluated for its paracetamol (640 mg/kg in 1% carboxy methyl cellulose)-induced hepatotoxicity in wistar rats. The methanol-treated group (200 and 400 mg/kg; p.o.) alleviated the toxic effects of paracetamol by restoring the levels of biochemical parameters such as total bilirubin, total protein, ALP, SGOT, and SGPT and by improving the levels of antioxidant enzymes. The presence of fatty acid infiltration, the absence of necrosis, and normal hepatic cords were observed in the histology of the extract-treated liver section that determined the hepatoprotective activity of the *E. neriifolia* extract.

Bigoniya and Rana [35] investigated the hepatoprotective activity of the saponin fraction containing euphol isolated from *E. neriifolia* leaf on CCL4-induced hepatotoxicity in rats. CCl4 is one of the hepatotoxic agents that causes peroxidation of the lipid membrane, resulting in hypoperfusion of the membrane. Decreased levels of SOD and elevated levels of ALP, SGOT, and SGPT was observed. Euphol pretreatment at 50, 125, and 175 mg/kg attenuated the CCl4-induced acute rise in serum ALP, SGPT, SGPT activities with reduced alterations in histological samples. Further saponin decreased the thiopentone directed sleeping time at 4 mg/kg; i.p. by protecting the metabolizing enzymes of the liver. This compound also replenished the decreased hepatic SOD and GSH by improving the antioxidant liver status. Moreover, it improved the cellular viability and bromsulphalein clearance. Thus, these natural compounds isolated from *E. neriifolia* provided protection against peroxidative damage directed by reactive oxygen species at the time of biotransformation induced by a hepatocarcinogen. Other pharmacological activities of *E. neriifolia* are listed in Table 9.

Table 9. Pharmacological activities of *Euphorbia neriifolia*.

Pharmacological Activity	Plant Parts	Mode of Actions	Dosage	References
Antioxidant activity	Leaf	Saponin showed better in vitro antioxidant activities compared to silymarin with a high bitterness index	10 mg/mL	[35]
	Leaf	Observed a good correlation among the antioxidant activity and physiochemical analysis and reported the maximum scavenging potential	1 mg/mL	[177]
	Leaf	FRAP method determined the reducing capability of ferric ions with 149.2 ± 0.05 µmol concentration. At 1 mg/mL of extract concentration, superoxide scavenging activity was determined to be 50.06% and it was 76.15% in the DPPH assay. The capacities for metal chelation of the standard and extract were 85.37% and 73.24%, respectively. The percentages of hydrogen peroxide scavenging potential of BHT, ascorbic acid, and extract were determined to be 44.7%, 12.7%, and 69.015%, respectively	1 mg/mL	[178]
	Leaf	In terms of metal chelation, reducing power, and scavenging activity, it was determined that the methanolic extract from different parts of *E. neriifolia* (leaves, stem, latex, and bark) possessed potential antioxidant activity	1 mg/mL	[179]
	Leaf	Showed effective DPPH scavenging activity	1 mg/mL	[91]
	Leaf	EN extract reduced the profile of serum lipid as well as of glucose by establishing its catabolic activity. It further raised the level of kidney and liver SOD along with catalase and decreased the lipid peroxidase in the liver. This represented that the *E. neriifolia* was considered to be safe and could be applied for the treatment of various ailments	400 mg/kg bw	[172]

Table 9. *Cont.*

Pharmacological Activity	Plant Parts	Mode of Actions	Dosage	References
Anti-diabetic activity	Stem	After administration of extract, there were decreases in fasting blood glucose level and in the oral glucose tolerance test after the time period of 60 min. The maximum reduction in the level of fasting blood glucose was found after 15 days of treatment at 400 mg/kg dosage. The profile of serum lipids was also found to be reduced compared to the control rat group	400 mg/kg bw	[103]
	Stem bark	It was found to suppress the levels of elevated blood lipids and glucose in diabetic rats. The results were determined to be comparable to the standard drug glibenclamide at 400 mg/kg of dosage. Thus, this study indicated the anti-diabetic and anti-hyperlipidemic activity of EN	100, 200, and 400 mg/kg bw	[180]
	Stem	The serum triglyceride, cholesterol, and blood glucose content were significantly ($p < 0.05$) decreased in treated group, whereas there was elevation in the serum HDL cholesterol levels in response to the methanolic extract of the *E. neriifolia* stem.	200 and 400 mg/kg bw	[180]
	Leaf	The ethanolic extract of *E. neriifolia* leaf with control produced 99.6 ± 2.540 mg/dl glucose drop at 400 mg/kg dosage after 60 min, whereas control resulted in 110.2 ± 3.01 mg/dl of glucose drop in streptozotocin-directed, high-fat diet type-2 diabetic animal model	400 mg/kg bw	[181]
	Leaf	The effect of ethanolic extract of *E. neriifolia* on glucose oxidase model was found to be 43.23 ± 3.58 mg/dl at 400 mg/kg, whereas control group has shown 112.63 ± 4.68 mg/dl of effectiveness	400 mg/kg bw	[172]
Immunomodulatory activity	Leaf	Significantly raised the phagocytic index, differential leucocyte count, and total leucocyte count to provide protection against abdominal sepsis. It increased the cell-mediated immunity and hemagglutination antibody titer by facilitating the footpad thickness response in betamethasone-induced and normal immunosuppressed rats. Therefore, it can be stated that *E. neriifolia* can be utilized as a complementary therapeutic agent for the treatment of immunomodulatory diseases	400 mg/kg bw	[110]
Anti-inflammation activity	Latex	Determined to have anti-inflammatory activity	400 mg/kg bw	[182]
	Leaf	EN caused inhibition in the inflammation of (1%) carrageenan-induced paw edema in rats	400 mg/kg bw	[26]
	Stem bark	These compounds result in the inhibition of pro-inflammatory mediators in cases of LPS-directed RAW264.7 macrophages. Studies on the cellular signaling pathway showed that these compounds prevent IkBα degradation and NF-kB/p65 subunit translocation. Furthermore, the amounts of COX-2, TNF-α, and PGE2 increased dramatically under the impact of these compounds, which was closely associated to the activation of the mitogen activated protein kinase (MAPKs) signaling pathway or by the phosphorylation of protein kinase C δ (PKCδ). Thus, these compounds have shown multidirectional regulation in the immune function of macrophages and cytokines, along with better anti-inflammatory activity with the close regulation of NF-kB and PKCδ/MAPKs signaling pathway	2.5 to 8 μM	[81]

Table 9. *Cont.*

Pharmacological Activity	Plant Parts	Mode of Actions	Dosage	References
	Latex	Determined to have potent anti-inflammatory activity in comparison to standard diclofenac sodium at 100 mg/mL dosage	750 and 500 mg/kg bw	[35]
Anti-arthritis activity	Leaf	Pre-treatment of this fraction significantly reduced the cytokine TNFα ($p < 0.05$) and paw edema ($p < 0.001$) in CFA-induced arthritic model after treatment for 28 days	–	[112]
Wound healing property	Leaf	Enhanced the epithelization. The content of protein and hydroxyproline was found to be increased along with the catalase activity, and the superoxide dismutase activity was determined in granular tissues.	200 and 400 mg/kg bw	
	Leaf	Showed efficacy of 100% and 85% in response to extract and control at 18th day in the excision wound model of rat	500 mg/kg bw	[183]
	Latex	Cutaneous wounds produced by surgery were treated tropically. Thus, the extract helped the healing process by increasing the angiogenesis, epithelization, DNA content, and tensile strength, respectively	1% and 0.5%	[184]
Anti-atherosclerosis	Latex	Modulated the pathway related to inflammation in order to relieve atherosclerosis	–	[185]
Radio-protective activity	Leaf	This compound exhibited moderate antioxidant activity with great reduction in the gamma-directed chromosomal abnormalities compared to gamma radiation alone. It also showed cytotoxic activity with an IC_{50} value of 173.78 µg/mL in a melanoma cell line. Thus, this compound can provide a scientific basis for the claim of radioprotective activity in EN	173.78 µg/mL	[186]
Anti-anxiety, anti-convulsant, anti-psychotic activity	Leaf	Significant reduction in the apomorphine-induced stereotype in rats and mice and absence of cataleptic effect that suggested the modulated activity of specific dopaminergic receptors	100, 200, and 400 mg/kg bw	[141]
Anti-thrombotic activity	Whole plant	The damage of the caudal vein was observed at 2 mg/kg dosage of carrageenan, whereas the ethanolic extract of *E. neriifolia* significantly ($p < 0.01$) reduced the thrombosis and increased the clotting and bleeding time of the animal	400 mg/kg	[144]
Dermal irritation	Latex	Inhibited the paw edema, which was induced by carrageenan	500 and 700 mg/kg bw	[35]
	Latex	Showed thrombolytic activity	_	[43]
Hemolytic activity	Leaf	Reported to have hemolytic activity at varied concentrations such as silymarin at 100 µg/mL of concentration, triton at 100 g/mL of concentration, and saponin at 300 µg/mL	300 µg/mL	[141]
Death receptor expression enhancing activity	Leaf	A novel ingol diterpene, 3-O-acetyl-8-O-tigloylingol (8), euphonerins A–G (1–7), and seven new cycloartane triterpenes were isolated from the methanolic fraction of *E. neriifolia* leaves, along with three known flavonols (11–13), (24R)-cycloartane-3β,24,25-triol (10), and 3,12-di-O-acetyl-8-O-tigloylingol. The structure of 1–8 compounds was made with the help of spectroscopic analysis. Among all compounds, 1–11 compounds have shown the death receptor expression enhancing activity	–	[88]
Analgesic activity	Leaf	The increase in reaction time in response to the *E. neriifolia* extract showed the better analgesic activity against thermal, chemical, and mechanical stimuli	100, 200, and 400 mg/kg bw	[187]

Table 9. *Cont.*

Pharmacological Activity	Plant Parts	Mode of Actions	Dosage	References
	Leaf	Showed analgesic activity against acetic-acid-induced abdominal constriction in mice	150, 300, and 400 mg/kg bw	[188]
Anti-diuretic activity	Leaf	Indicated in the increase in urine volume up to three times in response to the extract as an effective hypernatremic and hyperchloremic diuretic compared to control with 6.65 mL urine in model of rat	400 mg/kg bw	[149]
Anti-ulcer activity	Leaf	Showed anti-ulcer activity against ethanol-induced ulceration and pyloric-ligated ulceration	400 mg/kg bw	[189]
Anesthetic activity	Stem	Possessed good anesthetic activity in the case of the intradermal wheal in guinea pig and in the case of foot-withdrawal in frog	_	[151]
Anti-bacterial and Anti-fungal activity	Leaf	Exhibited greater anti-microbial activity against *Proteus vulgaris* with an 8 mm zone of inhibition	50 mg/mL	[190]
	Leaf	Showed anti-fungal activity against *Fusarium oxysporum* and *Candida albicans* with inhibition in their mycelial growth	50 mg/mL	[190]
	Stem	Found to be effective against *P. aeruginosa* at 400 mg/mL dosage, whereas it showed more effectiveness against *Staphylococcus aureus*	400 mg/mL	[154]
	Leaf	Inhibited the growth of *K. pneumonia* and *P. vulgaris*	50 µg/mL	[190]
	Latex	Found to be effective against *Klebsiella pneumoni* and *Salmonella typhi* with an 8 mm inhibition zone. It showed a 7 mm inhibition zone at 50 µL concentration against *P. aeruginosa*. MIC showed more effectiveness against *P. aeruginosa*, *K. pneumonia*, and *S. typhi* high concentration	60 and 50 µL	[191]
Anti-viral activity	Stem bark	Showed moderate anti-HIV-1 activities	24 and 34 mM	[83]
	Whole plant	Exhibited better anti-HIV-1 activity	6.4 and 6.6 µg/mL	[11]
	Whole plant	Exhibited moderate anti-HIV activity in comparison to standard azidothymidine	3.58 and 7.40 µM	[57]
	Leaf	Determined that the 3β-Friedelanol exhibited better anti-viral activity in comparison to actinomycin D (control) against HCoVs	_	[72]
Anti-asthmatic activity	Whole plant	EN ethanolic extract caused no toxicity, whereas ethyl acetate extract has shown the most significant anti-asthmatic property in all models	2000 mg/kg bw	[167]
Cytotoxic study	Leaf	Exhibited better cytotoxic activity against esophageal squamous cancer cells (KYSE-450 and KYSE-410 cells) and inhibited their proliferation	_	[192,193]
	Leaf	Showed in vitro cytotoxicity against the murine F1B16 melanoma cell line with 50% inhibition	173.38 µg/mL	[69]
	Latex	Inhibition against EAC cells and DLA cells	82 and 51 µg/mL	[174]
	Leaves and bark dried powder	In vitro anti-tumor activity with >50% inhibition rate in HepG2 cell line	89.25%	[174]
	Whole plant	Induced differentiation in megakaryocytic cells, inhibited growth, and caused apoptosis to some extent in HEL and K562 human leukemia cell lines	_	[174,193]
	Leaf	All compounds showed better cytotoxicity against the MCF-7 cell line	13.14, 7.12, and 9.50 µM	[174,193]

13. *Euphorbia neriifolia* as Petro-Crop

Recently, the value of medicinal plants that are capable of producing hydrocarbon has been increased incredibly. Some members in the family Euphorbiaceae were reported to have large amounts of hydrocarbons and extracts in comparison to other species of this family, which report low amounts of extracts and hydrocarbons due to the presence of water in large concentrations in its fresh form. The latex could be collected from the latex-containing Euphorbia species with the help of the lancing process, and then, these latex-containing plants were utilized as a promising petro-crop. The latex could be preserved or coagulated to form biocrude, as reported by Bhatia et al. [146]. This biocrude could be converted into petroleum hydrocarbon in the presence of a catalyst that can be utilized as a renewable source of hydrocarbon. Chemical and energy constituents for the formation of hydrocarbons from E. neriifolia were evaluated by Kalita and Saikia [147]. Thus, to meet the challenges of the rising demand of energy, large scale cultivation of E. neriifolia can occur on marginal or waste lands with low to poor water supply without much management and agricultural input.

14. Harmful Effects of *Euphorbia neriifolia* and Treatments

The E. neriifolia latex is considered to be toxic as it produces irritation and inflammation in the skin and eyes. Ocular toxic reactions may occur that range from mild conjunctivitis to severe kerato-uveitis. It may result in permanent blindness if it accidentally falls into the eyes. The injection of E. neriifolia latex may result in convulsion, a burning sensation in the stomach, vomiting, irritation, diarrhea, and coma [28]. The swallowing of the sap is also considered to be fatal because it results in perforation of the intestinal walls in the stomach and intestine and inflammation. The cytotoxic protein, euphorbon, that is present in E. neriifolia latex is more likely related to its toxicity, whereas the diterpenes such as phorbol, ingenol, and 12-deoxyphorbol are responsible for various biological activities. The E. neriifolia plant is poisonous and the contact of sap with skin may result in blistering. The roots and leaves are utilized as a fish poison [28].

14.1. Treatment

Wash out the contacted area with running water.

14.1.1. Symptomatic Treatment

On ingestion: gastric lavage with normal saline and activated charcoal.

14.1.2. On Contact

Skin—Topical corticosteroids.

Eye—Intra ocular pressure (IOP) lowering medications, tear substitute, and antibiotic eye drops [21,28,193,194].

15. Summary and Conclusions

The research on medicinal plants is increasing not only to prevent sudden outbreaks or antibiotic resistance but to provide safer medicines rather than synthetic ones. From the above discussion, it is clear that in alternative system of medicines, E. neriifolia or its extracts have potential to be used in several pathologies, such as E. neriifolia leaf for tumor, bronchial infection, etc.; E. neriifolia stem for hydrophobia; E. neriifolia latex for asthma, leprosy, etc.; and E. neriifolia roots for snake bites and scorpion stings that cannot be treated by modern methods. E. neriifolia is a good source of phytochemicals such as eupnerias G-I, eurifoloid M, neriifolins A–C, phorneroids A–M, neritriterpenols A–G, tulipanin, euphol, etc., that support its ethno-botanical significance (such as antioxidant, anti-diabetic, immunomodulatory, anti-inflammatory activities, etc.). However, in spite of the various applications of EN, it is surprising to know that because of some toxicity, this plant is not favorable for its uses. The nature and the mechanism of action of its toxic chemicals remained undiscovered until the present. From the thorough study and

investigation of the available literature on EN, it was easy to determine that this plant is a rich source of various phytocompounds that are therapeutically efficient for the treatment of several health related issues since pre-historic times, and this provides a wider zone of interest for the discovery of new molecules for drugs, and their mechanism of treatment should be established.

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