Biomedical Research and Therapy, 2022; 9(2):4930-4949

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Review

Euphorbia hirta as a gold mine of high-value phytochemicals: A comprehensive review of its pharmacological activities and possible role against SARS-CoV-2

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ABSTRACT

Euphorbia hirta is a common medicinal plant in folk and traditional medicine systems. This plant has shown promising effects against several human ailments and infectious diseases. Therefore, it is important to summarize the medicinal activities and value of *Euphorbia hirta*. The main intent of this literature review was to summarize the phytochemical content and pharmacological applications of *Euphorbia hirta*. The literature review about the pharmacology and phytochemistry of *Euphorbia hirta* was collected from different global platforms, such as Scopus, ERIC, PubMed, and Web of Science. *E. hirta* has a rich phytochemistry and exhibits remarkable activity against respiratory diseases, gastrointestinal disorders and venereal diseases. Different extracts of this plant have shown significant preclinical anticancer propensity against an array of different cancer cell lines. It acts as a highly active antiviral agent and has shown pronounced activity against coxsackievirus, human immunodeficiency virus, dengue virus, poliovirus and simian immunodeficiency virus. A clinical study showed its inhibitory responses against flu and fever in dengue patients. Most importantly, the plant possesses remarkable inhibitory action on ACE, which aids SARS-CoV-2 entry into host cells. The multidimensional role of *Euphorbia hirta* as a potential antiviral agent suggests its possible application to control COVID-19 along with modern and Western medicinal strategies. In conclusion, the literature review regarding *Euphorbia hirta* showed its strong pharmacological applications, such as antimicrobial, antimalarial, anti-asthmatic, antioxidant, antiviral and anticancer activities. Further in-depth research is necessary to monitor its role in the management of viral diseases, especially COVID-19.

Key words: ACE-2, Ethnopharmacology, Euphorbia hirta, Phytochemistry, SARS-CoV-2

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History

- Received: Nov 26, 2021
- Accepted: Jan 30, 2022
- Published: Feb 28, 2022

DOI : 10.15419/bmrat.v9i2.728

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INTRODUCTION

Euphorbia hirta is frequently known as "Asthma plant" in English and "Dudhi" in Hindi. The plant is widely distributed throughout the globe, and in Asia, it is mainly found in Yemen, Oman, Palestine, Taiwan, Syria, Lebanon, India, Bhutan, Pakistan, Nepal, Myanmar, Thailand, Sri Lanka, Indonesia, Malaysia, Papua New Guinea and the Philippines[1]. The plant belongs to the genus Euphorbia family of Euphorbiaceae. The morphological features of *E. hirta* include a slender stem with hair development and many branches arising from it from base to top. The plant is annual purple or reddish in color and attains a height of approximately 40 cm. The leaves of the plant grow oppositely and are elliptical-oblong to oblong-lanceolate in shape. The leaves measure up to 1 – 2.5 cm in length with green color on the top side and pale color on the bottom side. The fruits are three-celled, yellow, keeled capsules, hairy, 1 - 2 mm in diameter, containing four-sided, three brown, wrinkled, angular, seeds[2–5]. The plant *Euphorbia hirta* has long served humanity in the form of traditional and folk medicine. In addition to *Euphorbia hirta*, other species of the genus Euphorbia also show medicinal importance and are being used in traditional medicine. A milky juice comes out of all the species of Euphorbia upon breaking, and this juice is considered to be more/less toxic and hence was used on arrows for hunting purposes in old times[6]. *Euphorbia hirta* is a high-value medicinal plant possessing significant antimalarial, antifungal, antifertility, antispasmodic, sedative, antiasthmatic, anthelmintic and antibacterial properties[2]. Additionally, the plant has been found to have significant anticancer effects against a variety of aggressive cancer cells.

This review aims to summarize the phytochemical compositions and pharmacological activities of *Euphorbia hirta* and tries to bridge the possible role of *Euphorbia hirta* in the management of COVID-19, a going on global pandemic. Respiratory tract exposure to the external environment leads to high communicability of the disease. SARS-CoV-2 pa-

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Cite this article : Khursheed A, Jain V, Wani A R. ***Euphorbia hirta* as a gold mine of high-value phytochemicals: A comprehensive review of its pharmacological activities and possible role against SARS-CoV-2**. *Biomed. Res. Ther.,* 2022; 9(2):4930-4949.

tients differ in clinical symptoms some show evident symptoms, and some remain asymptotic[7]. Asymptomatic patients with SARS-CoV-2 viral loads are the most active transporters leading to the fast spread of the disease because these patients are not aware of the disease until advanced stages. The initial clinical symptoms involve chills, fever, fatigue, cough, diarrhea, shortness of breath and respiratory symptoms. The generation of potential vaccines or capable drugs against SARS-CoV-2 infection is the global emergency right now. Unfortunately, the development of vaccines or potential drugs may take a longer time. Therefore, intermediate treatment methodologies are needed to address this global health issue. The government of the Republic of China is currently emphasizing Traditional Chinese Medicine (TCM) in controlling SARS-CoV-2 infection[8,9]. Several clinical trials have already been initiated to study the efficiency of TCM against SARS-CoV-2 infection. In certain cases, patients along with Western medicine were sidewise supplied with TCM. The results showed that TCM induced synergistic effects with Western medicine against SARS-CoV-2[10]. Treatments with medicinal plants and herbs are mostly symptoms and sign based. Herbal medicines with potential efficacy against specified targets against viruses could be evaluated for their activity against SARS-CoV-2, reliant on signs and symptoms[11,12]. The prime focus of this review was to summarize the phytochemical constituents and pharmacological and medicinal importance of *Euphorbia hirta* along with assessing its possibility to be used against COVID-19.

Figure 1: ***Euphorbia hirta* .**

EUPHORBIA HIRTA

E. hirta Linn. (**Figure 1**) is a small annual, branched herb that can grow to 70 cm in height, purple or reddish in color with copious amounts of latex, and covered with sprout hairs.

Leaves: The leaves are opposite, biculate and simple, the stipules are linear, the leaf blade is lanceolate, oblong serrate, long elliptic, tapering, 3 – 4 cm long and 1 – 1.4 cm wide, and its margin is smoothly serrated.

Flowers: The monoecious inflorescence, an axillary or terminal cluster of flowers, is known as a cyathium, in which several cyathia are arranged in a cyme. The male and female flowers are in a pod and both appellation. The flowers are unisexual, male flowers are sessile, prophylls are linear, fringed, perianth absent and have a stamen, female flowers have a small peduncle, the perianth is fringed, the ovary is covered with tiny hairs above, 3-celled, has 3 - Styles, small and the tip is double. The flowering period is usually year round.

Fruit: The fruit is allomorphic, pistillate, elongated, 3-lobed, obtuse base covered with shoot hairs.

Seeds: Seeds are oblong, 4-sided prismatic, wrinkled and brownish pink in color, capsule 3-seeded, green and covered with fleshy spines, seeds smooth, hard mottled crustal skin with a white caruncle at the top enclosing oily endosperm[13–19].

Roots: The root is a distinct and developed primary root (taproot system).

Classification: *E. hirta Linn.* belongs to the Euphorbiaceae family, known as the Spurge family. It is the largest family, consisting of almost 300 genera and 5000 species. Euphorbia is the largest genus of the Euphorbiaceae family and includes approximately 1600 species.

BIOACTIVE SECONDARY METABOLITES FROM *EUPHORBIA HIRTA*

Plants are a source of highly active biological principles, making them helpful to humanity in regard to tackling key issues, including health[20,21]. The plant bears a wide variety of phytochemicals, including reducing sugars, alkaloids, terpenoids, flavonoids, tannins, steroids, fats, proteins, gums, oils, mucilage, saponins, glycosides, cardiac glycosides, coumarins, anthraquinones and phenolic compounds[22]. Some of the important phytochemical constituents are summarized in **Figure 2**. The methanolic extract of *Euphorbia hirta* has been identified with ten compounds, including palmitic acid, chloromorpholin-4-ium, S-methyl-L-cysteine, nicotinic acid, methyl 14-methylpentadecanoate, 2,3,5-trimethyl-1 H-pyrrole, 5-methyl-1,3-oxazolidin-2-one, 2-amino-3-sulfanylpropanoic acid, 17-carboxyheptadec-9-en-1-ylium and 4-amino-4-oxobut-2-enoic acid[23].

Kingdom	Plantae
Division	Spermatomatophyta
Class	Dicotyledonae
Order	Euphorbiales
Family	Euphorbiaceae
Genus	Euphorbia
Species	Hirta

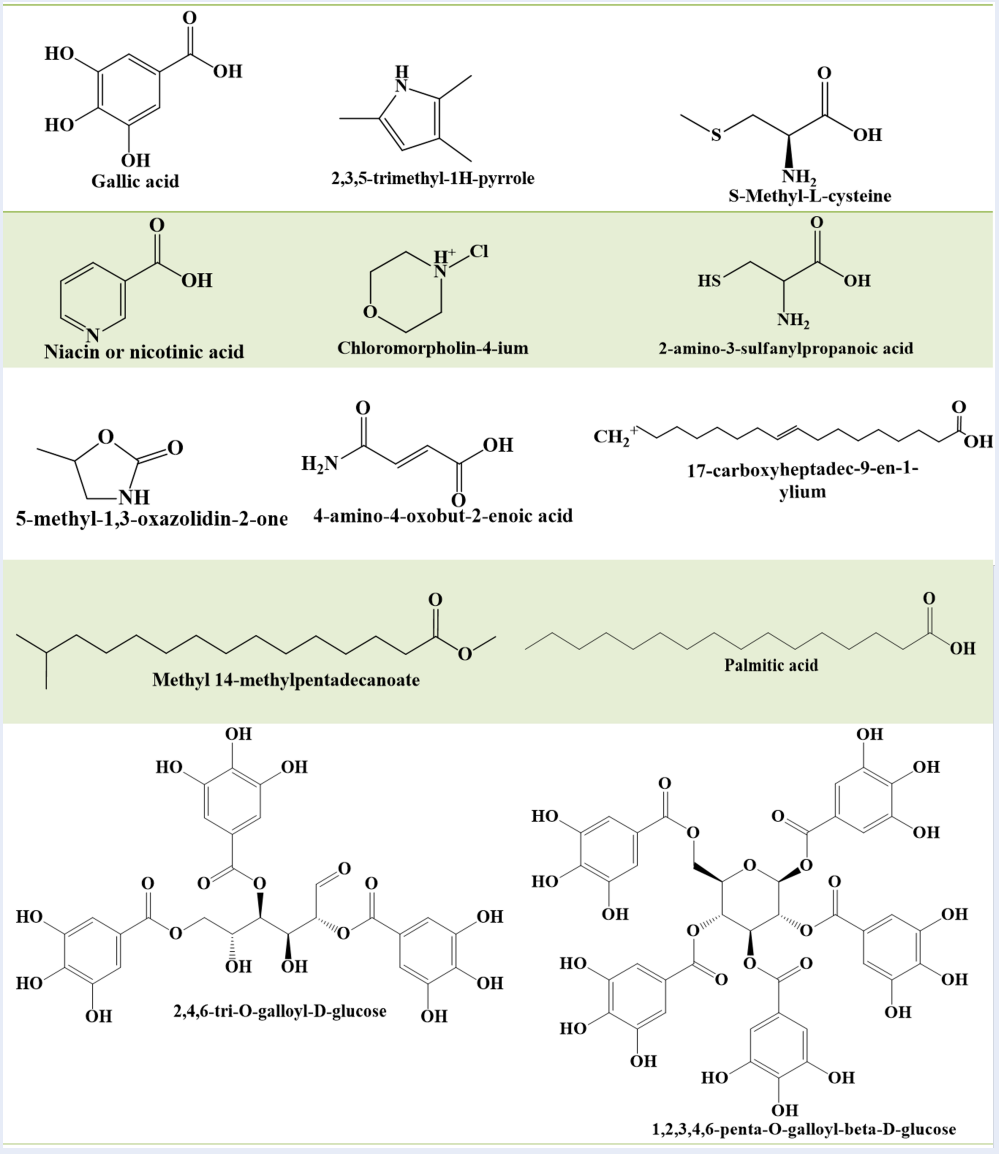

Figure 2: **Structure of some of the phytochemical constituents from *E. hirta*.**

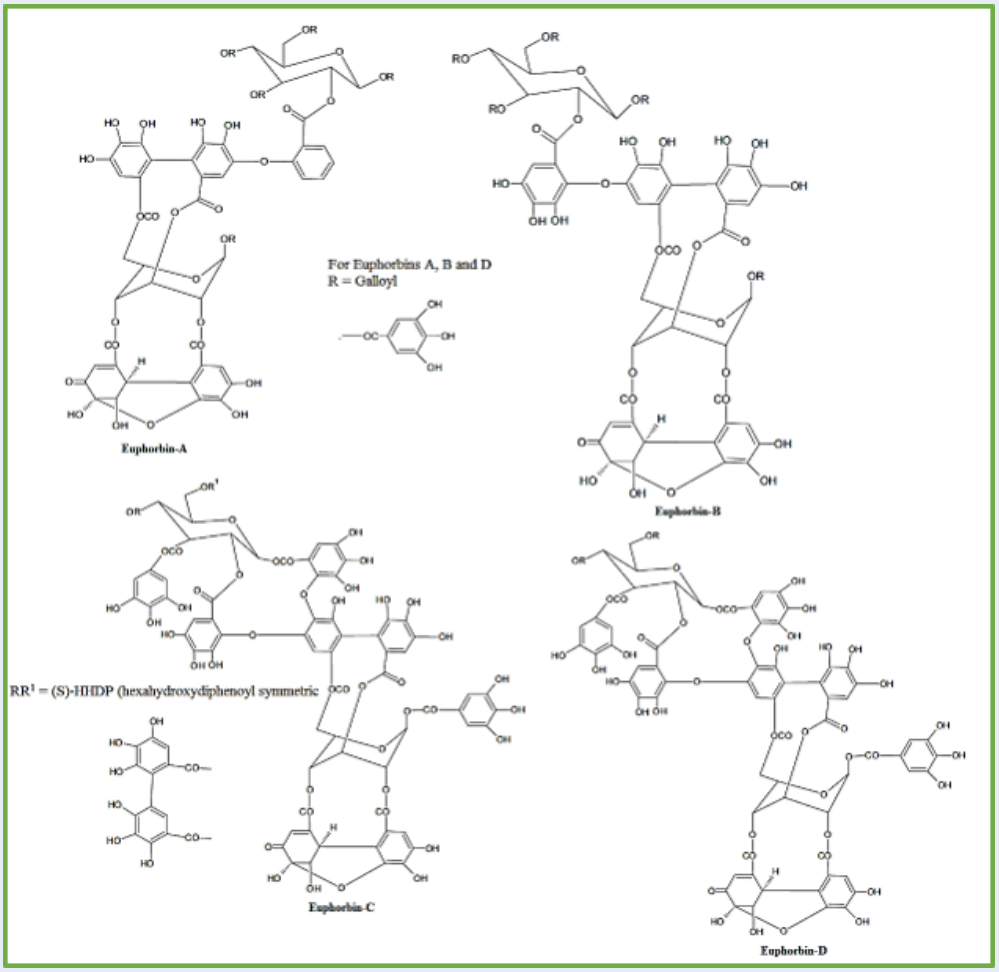

Figure 3: **Euphorbins (A-D) from *E. hirta*.**

Six compounds were identified and isolated from *E. hirta* leaves: 3,4-di-*O*-galloylquinic acid, gallic acid, myricitriu, quercitrin, 1,2,3,4,6-penta-*O*-galloyl-beta-*D*-glucose and 2,4,6-tri-O-galloyl-D-glucose[24]. Aerial parts of the plant were identified with quercitrin, afzelin, 1,3,4,6-tetra-O-galloyl-β-d-glucose, 2,4,6-tri-O-galloyl-β-d-glucose, euphorbins A-D (**Figure 3**), myricitrin, kaempferol, rutin, quercetin, gallic acid, and protocatechuic acid[25]. Furthermore, 11α,12α-oxidotaraxerol, α-amyrin, β-amyrin, taraxerone, β-amyrin acetate, taxerol, tannins and taraxerone have been reported from plants. Moreover, β-sitosterol, α-amyrin, 24-methylencycloartenol, camphol, leucocyanidol, euphorbianin and euphorbins A-E have also been isolated from the plant.

MEDICINAL PROPERTY OF *EUPHORBIA HIRTA*

Different parts of *E. hirta* have shown numerous pharmacological and biological properties. The high biological value of the plant is primarily attributed to its high diversity in phytochemical content. Some of the biological activities are represented in **Figure 4**.

Ethnopharmacology

E. hirta has a very high medicinal value. Ethnopharmacologically, *E. hirta* is used to cure respiratory and bronchial disorders (hay fever, bronchitis and asthma), conjunctivitis and gastrointestinal diseases such as intestinal parasitosis, dysentery and diarrhea. Furthermore, *E. hirta* shows significant tonic and hypotensive properties[26]. Stem sap of *E. hirta* is used to cure eyelid styes caused by bacterial infection, and leaves are used against boils and swellings by mak-

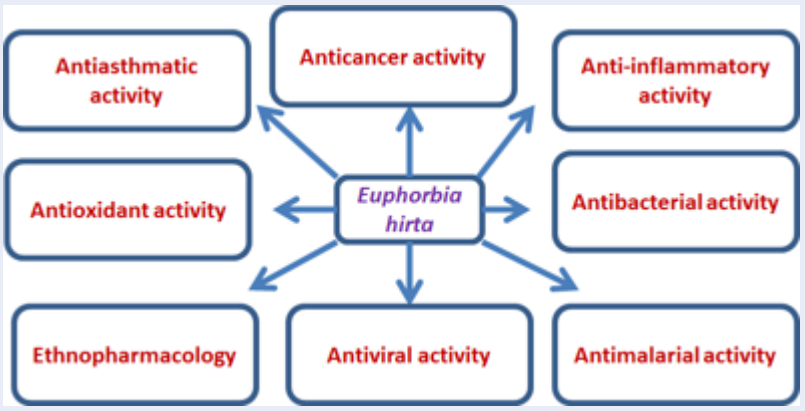

Figure 4: **Biological activity profile of *Euphorbia hirta*.**

ing their poultice. The plant as a whole is used by humans against different diseases, such as fresh herb decoction in the treatment of thrush by gargling, dry decoction to cure skin disorders and decoction of roots, which is implemented in snake bites and for milk production in nursing mothers[27]. Antispasmodic and antiamoebic activities have been shown for polyphenolic extracts of the plant[28,29]. Furthermore, the *E. hirta*-isolated compound quercitrin has been reported to have remarkable antidiarrheal potential[30,31]. It shows reflexive effects on cardiovascular systems in humans, such as the respiratory system[32]. The *E. hirta* plant alcoholic extracts show tranquilizing effects on the genitor-urinary tract and report hypoglycemic effects in rats[33,34]. The isolated compounds and solvent extracts of *E. hirta* demonstrated substantial anticancer activities. *E. hirta* extracts exhibit inhibitory effects on prostaglandin release, including D2, E2 and I2. It has also been reported to produce protective effects against contamination caused by aflatoxin in mustard, rice, maize and wheat crops[35]. Methanolic extracts of *E. hirta* leaves have been shown to have strong antibacterial and antifungal properties. Itchy soles are treated by pounding, warming and rubbing the leaves of *E. hirta* with coconut oil and turmeric. Plant latex is used to cure eye sores by applying it to the surma on the lower eyelids. A number of the ethnopharmacological uses of *E. hirta* are listed in **Table 1**.

Antibacterial activity

Ethanolic extraction from *E. hirta* leaves has been tested for its antibacterial activities against *Salmonella typhi, Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli*. The extract showed strong inhibition of all these bacteria except *Salmonella typhi*. The minimum inhibitory values were calculated to be 74.61, 57.64, 22.55 and 54.09 mg/ml for *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli*, respectively[36]. Unlike solvent extractions from the stem, bud and leaves of *E. hirta*, their antimicrobial effects against *Staphylococcus aureus* were evaluated using the disc-diffusion method. The methanolic extract from leaves and bud exhibited very strong activity against *S. aureus* , with a zone of inhibition score of 20 mm and a zone of inhibition area score of 471.00 mm^2 [37]. Chloroform and aqueous fractions of *E. hirta* L. leaves have been reported to possess noncytotoxic but antibacterial effects against *Klebsiella pneumonia*[38].

Anti-inflammatory activity

The medicinal herb *E. hirta* has been reported to have remarkable anti-inflammatory effects. In a study, the aqueous and ethanolic extracts of *E. hirta* were evaluated for their anti-inflammatory activity against carrageenan-induced inflammation in rats. It has been shown that both extracts produced substantial anti-inflammatory effects against the reference drug diclofenac sodium (50 mg/kg)[39]. In a similar study, the lyophilized aqueous extract from *E. hirta* has been reported to suppress inflammation in carrageenan-induced rats starting from the concentrations of 100 mg/kg of body weight[40]. Furthermore, *n*-hexane extracts from *E. hirta* have been shown to inhibit inflammation in mouse models of phorbol acetate-induced ear inflammation[41]. The anti-inflammatory effects were found to be concentration-dependent. In another study, fractionated *Euphorbia hirta* aqueous extract showed *in vitro* anti-inflammatory activity on rabbit synovial fibroblasts[42].

Table 1: Pharmacological activities of *E. hirta*

No	Activity	Action
1	Anti-allergic activity	The ethanolic fraction of *E. hirta* induces inhibitive effects on the discharge of IL-6 and TNF-α in anti-DNP-HAS activated rat peritoneal mast cells.
2	Antibacterial activity	Different solvent extracts from *E. hirta* were evaluated for antibacterial effects *Bacillus subtilis, Pseudomonas. aeruginosa, Staphylococcus aureus*, and *Escherichia coli*. The results demonstrated outstanding antibacterial property of *E. hirta* against these pathogen bacteria.
3	Anti-diabetic activity	The solvent extracts of stem, flower and leaf of *E. hirta* showed lowering effects on overall blood glucose levels on administration to streptozotocin induced diabetic mice.
4	Anti-diarrheal activity	The leaves of *E. hirta* are rich in flavonoids content especially the quercitin molecule has been shown to exhibit anti-diarrheal effects through enhancement in the absorption of colonic fluid in presence of secretagogue compounds.
5	Antioxidant activity	Antioxidant activity of *E. hirta* was shown by performing FRAP and DPPH assay and outcomes demonstrated remarkable antioxidant potential of methanolic extract of *E. hirta* by acting against oxidative damage to protein.
6	Antitumor activity	Research has shown that the methanolic extract of *E. hirta* induce antiproliferative effects in Hep-2 cells isolated from human epithelioma of larynx. Hence, predicting antitumor potency of *E. hirta*.
7	Anxiolytic and sedative activity	The antagonists of the GABAA receptor-benzodiazepine receptor-Cl channel complex with *E. hirta* were used together, and anxiety in the EPM showed marked anti-anxiety activity in chronic immobilization stress
8	Diuretic activity	The *E. hirta* ethanolic extract on administration to rats augmented the total urine excretion thus improving diuresis.

Antioxidant activity

E. hirta possesses strong antioxidant activities in both animal models and *in vitro*. It has been shown to have strong free radical scavenging potency in various experimental models using hydroxyl radical scavenging, ABTS, and DPPH assays. The free-radical scavenging ability of the methanolic extract of *E. hirta* was investigated. The results reported that the methanolic fraction of *E. hirta* leaf extract produced a tremendous DPPH inhibition of 71.96±0.78%. The increasing order of DPPH scavenging activity of *E. hirta* was stems (44.42±0.94%) < roots (48.59±0.97%) < flowers (52.45±0.66%) < leaves. The IC_{50} values calculated for stems, roots, flowers and leaves were 1.358, 0.989, 0.972 and 0.803 mg/mL, respectively[43]. Another study carried out by S. Asha and coworkers reported significant antioxidant activity for *E. hirta*. They showed antioxidant activities for three types of extractions from *E. hirta* through superoxide, DPPH and hydroxyl radical scavenging assays. Out of the three extracts (ethanolic, methanolic and aqueous), the ethanolic extract exhibited the highest antioxidant propensity with a significant IC_{50} value compared to the methanolic and aqueous extracts. Furthermore, a significant relationship was obtained between the phenolic content of the extracts and antioxidant activity, and the ethanolic extract showed a high phenolic content[44]. *E. hirta* showed maximum free radical scavenging and antioxidant activities at approximately 0.25 mg/ml.

Anticancer activity

Several traditionally used medicinal plants are thought to have preventive effects against different human malignancies, including cancer. These plants are rich in chemical contents that show modulatory effects on different physiological functions and target the proliferation of cancer cells. *E. hirta* has been reported to produce significant anticancer effects *in vitro* against acute myeloid leukemia HL-60 cells[45]. Furthermore, extracts from *E. hirta* have revealed anticancer effects against squamous cell carcinoma, Hep-2 and malignant melanoma[46,47]. Shao-Ming Chi et al., 2012 isolated (1'R,5'R)-5-(5'carboxylmethyl-2'-oxocyclopentyl)-3Z-pentenyl acetate, a cyclopentanone derivative from *Euphorbia hirta*. The ethanolic extract was examined for cytotoxicity against the K562 and A549 cell lines.

The outcome of the study revealed weak cytotoxicity against A549 cells (15.02 ± 11.60%) and remained almost inactive against K562 cells[48]. Sandeep *et al.* in 2011 evaluated the antitumor properties of *E. hirta*[49]. Aerial parts of *E. hirta* were extracted using different solvents, including chloroform, ethanol and petroleum ether, and showed positive results for the presence of alkaloids, tannins, saponins, and flavonoids. The ethanol and chloroform extracts were reported to maximize the mean survival and inhibit the growth of solid tumors in administered mice. This antitumor activity was attributed to the manifestation of flavonoids.

Antimalarial and anti-asthmatic activities

Euphorbia hirta has been reported to contain a pool of active phytochemicals that raise the medicinal value of the plant. *Euphorbia hirta* has been termed an "Asthma plant". It shows depressant effects on the respiratory system and reflexive effects on brochial tubes[32]. Additionally, methanolic extraction from aerial parts of *Euphorbia hirta* by bioassay-guided fractionation has been evaluated for antiparasitic activity against *P. falciparum*. The key chromatographic fraction has been reported to show over 90% inhibition at 5 μg/ml against *P. falciparum*[50].

Table 2: List of some of the common medicinal and aromatic plants with potential antiviral properties [51]

Family	Plant Species	Mode of Action	Plant Part	Origin
Acanthaceae	Andrographis paniculata	Antiviral	Leaves	India, Sri Lanka
Acanthaceae	Strobilanthes cusia	Inhibits HCoV-NL63 via tryptanthrin; anti-influenza virus activity; anti-inflammatory potential	Leaves, Whole plant	Tropical Asia, Madagascar
Adoxaceae	Sambucus nigra	Antiviral activity against HIV, HSV, influenza, hepatitis, and coxsackievirus	Whole plant	Europe and North America
Adoxaceae	Viburnum opulus	Immunomodulation; anti-inflammatory effects	Fruits	Western and eastern, Siberia Eastern Europe, Caucasus, and Central Asia
Alliaceae	Allium sativum	Inhibits avian coronavirus; antiviral, fungistatic	Bulb	Central Asia, Iran
Anacardiaceae	Rhus coriaria	Antiviral potential	Fruit	Mild Mediterranean climates of western Asia and southern Europe
Apiaceae	Ferula assa-foetida	Antiviral activity; great potency against H1N1; anti-inflammatory	Oleo-Gum-resin	Iran, Afghanistan
Apiaceae	Saposhnikovia divaricata	High antiviral activity against PEDV corona-virus	Whole plant	China
Apocynaceae	Aspidosperma sp.	Antiviral activity against avian metapneumovirus and other groups	Whole plant	South America
Apocynaceae	Gymnema sylvestre	Inhibition of viral DNA synthesis; immunomodulation	Leaves, Whole plant	Asia, Africa, Australia
Araliaceae	Oplopanax elatus	Immunomodulation and anti-inflammatory activities	Whole plant	North America, northeastern Asia
Asteraceae	Anthemis hyalina	Inhibits coronavirus replication and expression of transient receptor potential gene family	Whole plant	Mediterranean region, south-west Asia to Iran
Asteraceae	Artemisia sp. (Artemisia absinthium)	Reduces coronavirus replication; antibacterial, anti-inflammatory	Whole plant	Eurasia, north Africa, North America
Asteraceae	Cichorium intybus	Immunomodulation; antiviral action against adenovirus type and 5HSV-1	Whole plant, Roots	Eurasia, Mediterranean region
Asteraceae	Cynara scolymus	ACE inhibitor, antiviral	Flower heads	Mediterranean region

Continued on next page

Table 2 continued

Family	Plant Species	Mode of Action	Plant Part	Origin
Asteraceae	Echinacea angustifolia	Antiviral activity against cold and flu viruses; inhibits discharge of pro-inflammatory cytokines and viral growth.	Flowers	North America
Asteraceae	Echinops sp.	Antiviral, cough suppressant	Trehala manna	Iran
Asteraceae	Inula helenium	Anti-inflammatory	Rhizomes, Roots	Caucasus, Eastern Europe, western Siberia, Central and Far East Asia
Asteraceae	Rhaponticum carthamoides	Immunomodulation	Roots	Southern Siberia, Kazakhstan, Altay region
Asteraceae	Sphaeranthus indicus	Antiviral activity against mouse coronavirus; anti-inflammatory and bronchodilation	Whole plant	Northern Australia, Indo-malayan realm
Bignoniaceae	Arrabidaea samydoides	Antiviral activity against HSV-1, vaccinia virus and murine encephalomyocarditis virus	Whole plant	South America
Bignoniaceae	Tabebuia sp.	Antiviral potential	Whole plant	South America
Boraginaceae	Echium amoenum	Antiviral	Flowers	Iran, Caucasus, Russia
Brassicaceae	Isatis tinctoria	Inhibits cleavage activity of SARS-3CLpro enzyme; anti-inflammatory and strong antioxidant potential	Roots extracts	Caucasus, Central Asia, eastern Siberia, western Asia
Cannabaceae	Humulus lupulus	Immunomodulation; antiviral activity against cold and influenza viruses, herpesvirus and hepatitis C; inhibition of virus replication	Inflorescences	North America, Europe, western Asia
Crassulaceae	Bryophyllum pinnatum	Anti-inflammatory, immunomodulator	Whole plant	Madagascar
Cupressaceae	Juniperus communis	Prevents replication, 3CLpro; antiseptic and anti-inflammatory	Fruits	Europe, North America, Asia
Cupressaceae	Thuja occidentalis	Immunostimulation; antiviral activity against acute common cold	Leaves Whole plant	Upper northeastern, North and Central United States and Eastern Canada

Continued on next page

Table 2 continued

Family	Plant Species	Mode of Action	Plant Part	Origin
Elaeagnaceae	Hippophae rhamnoides	Anti-influenza activities and Immunomodulation	Fruits	Cold-temperate regions of Europe and Asia
Euphorbiaceae	Euphorbia sp.	Antiviral activity against SIVmac251, HSV-2, HIV-1 and HIV-2	Roots	North and South America, Southern Africa and Madagascar, Mediterranean region
Fabaceae	Acacia nilotica	Inhibits HIV protease; cytotoxic and antiviral	Whole plant	Indian subcontinent, Middle East and Africa
Fabaceae	Alhagi maurorum	Inhibits influenza and cold viruses; relieves cough, pectoral aches, fever, vomiting and thirst	Gum tragacanth	South-east Europe, south-west Asia
Fabaceae	Clitoria ternatea	Antiviral	Whole plant	Indian subcontinent, Southeast Asia
Fabaceae	Desmodium canadense	High antiviral activity toward coronaviruses	Whole plant	North America
Fabaceae	Glycyrrhiza glabra	Immunomodulation; antiviral activity against human cytomegalo-virus, Epstein–Barr virus, HSV-1, and RNA viruses including H1N1, influenza A, and H5N1	Roots	Mediterranean area, Iran-Turan, Azerbaijan
Geraniaceae	Pelargonium sidoides	Decreases rhinovirus infection through regulation of binding viral proteins in bronchial cells.	Leaves, Whole plant	South Africa
Hypericaceae	Hypericum connatum	High antiviral activity	Whole plant	North America, eastern Asia
Lamiaceae	Mentha piperita	High antiviral activity against coronavirus group	Whole plant	Europe, Middle East
Lamiaceae	Mosla sp.	Anti-influenza activity	Whole plant	Eastern and southeastern Asia, Himalayas
Lamiaceae	Ocimum kilimandscharicum	Antiviral activity against HIV-1, SARS-CoV-2	Whole plant	Central Africa, Southeast Asia
Lamiaceae	Origanum vulgare	Respiratory and antiviral activity	Leaves, Stems	Mediterranean region, Southwestern and Western Eurasia

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Table 2 continued

Family	Plant Species	Mode of Action	Plant Part	Origin
Lamiaceae	Rosmarinus officinalis	Antiviral activity against human respiratory syncytial virus; immunomodu-lator; anti-inflammatory	Whole plant	Mediterranean region
Lamiaceae	Salvia officinalis	High binding to COVID-19 proteases; Inhibits HSV-1 and SARS-CoV replication	Whole plant	Mediterranean basin
Lamiaceae	Scutellaria baicalensis	Inhibit nsP13 by affecting the ATPase activity	Roots	China, Korea, Mongolia, Russian far east, Siberia
Lamiaceae	Stachys schtschegleevii	Antiviral, anti-inflammatory and anti-SARS-CoV-2	Leaves	Iran
Lamiaceae	Thymus vulgaris	High antiviral activity toward coronaviruses; antioxi-dant effects	Whole plant	Southern Europe
Lauraceae	Cinnamomum cassia	Antiviral, anti-inflammatory; inhibits attachment of human respiratory syncytial virus	Bark	Vietnam and eastern Hi-malayas, China
Lythraceae	Punica granatum	Inhibits viral glycoproteins; antiviral action against in-fluenza virus and HSV-1	Fruits, Peel, Seeds	Iran to northern India, Mediterranean region
Malvaceae	Althaea officinalis	Anti-inflammatory in diseases of the upper respiratory tract; antitussive, chest emollient, immuno-modulator, antiviral	Whole plant	Western palearctic, boreal area, Europe, Asia and Africa
Malvaceae	Firmiana simplex	Immunomodulation; general tonic and adaptogenic drug	Leaves	South Japan, China and In-donesia
Menispermaceae	Stephania tetrandra	Inhibits expression of HCoV-OC43 nucleocapsid and spike proteins; anticancer and immunomodulatory po-tential	Roots	China, Taiwan
Plantaginaceae	Plantago major	Anti-inflammatory; antiviral activity against her-pesviruses and adenoviruses	Leaves, Whole plant	Europe, Northern and cen-tral Asia
Ranunculaceae	Nigella sativa	Antiviral activity against avian influenza virus (H9N2), Immunomodulator, broncho-dilator and anti-inflammatory agent	Whole plant	Eastern Mediterranean, northern Africa, Indian Subcontinent, western Asia
Rhamnaceae	Ampelozizyphus amazoni-cus	Immunomodulation, anti-inflammatory	Whole plant	South America

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Table 2 continued

Family	Plant Species	Mode of Action	Plant Part	Origin
Rhamnaceae	Ziziphus jujuba	Antiviral activity; potential therapeutic agent for treating influenza	Fruit	Southeastern Europe to China
Rosaceae	Rubus sp.	Antiviral effect against human influenza virus	Fruits, Flowers	Forest-steppe zones of Eurasia
Rosaceae	Rosa sp.	Immunomodulatory effects; antiviral activity against HIV and HSV	Completely matured fruits	Europe, North America, Northwestern Africa
Rutaceae	Citrus trifoliata	Antiviral against oseltamivir-resistant influenza virus	Seeds	Northern China and Korea
Sapindaceae	Litchi chinensis	The plant inhibit SARS-3CLpro, while the isolated terpenoids suppress HIV-1 protease	Seeds	Southeastern China
Saururaceae	Houttuynia cordata	Inhibits viral tRNA polymerase (RdRp) and SARS-3CLpro activity; activates IL-2 and IL-10 secretion	Whole plant	Southern Asia
Solanaceae	Hyoscyamus niger	Viral inhibition; bronchodilator; antiviral effect against human influenza virus A/WSN/33	Whole plant	Middle East, Asia, Continental Europe
Theaceae	Camellia japonica	Strong inhibition of a member of coronavirus family that is porcine epidemic diarrhea virus through suppression of important protein and gene synthesis during replication	Whole plant, Flowers	East Asia
Urticaceae	Urtica dioica	Inhibition of SARS coronavirus replication	Leaves	Europe, temperate Asia, and western North Africa
Verbenaceae	Vitex trifolia	Strongly antiviral against and mouse coronavirus HSV, anti-inflammatory effects on lungs, immunomodulatory	Whole plant	French Polynesia, Tropical East Africa
Zingiberaceae	Zingiber officinale	Inhibition of syncytial virus effecting human respiratory	Rhizome	Asia, Maritime Southeast
Zosteraceae	Zostera marina	Strongly antiviral against influenza A virus	Whole plant	North America, Europe, Asia

Antiviral activity of *Euphorbia hirta*

Medicinal and aromatic plants have been a rich reserve for antiviral agents since time immemorial. Some of the medicinal plants with antiviral activity are listed in **Table 2.** *Euphorbia hirta* is a medicinally as well as biologically important plant. It has been used to treat a wide variety of disorders since time immemorial[52]. *Euphorbia hirta* has been a foremost important constituent of traditional systems of medicines, including Ayurveda medicine and TCM. It is used for the management of respiratory diseases, gastrointestinal disorders, venereal diseases, sterility, menstrual problems, kidney stones, colds, coughs, emphysema, laryngeal spasms, hay fever, bronchitis, asthma, amoebic dysentery, vomiting, heartburn, peptic ulcers, diarrhea, and intestinal parasites[53–58]. Gyuris *et al.* evaluated the *Euphorbia hirta* extract for its antiretroviral potency against T lymphocyte MT4 cells. The effects of aqueous and methanolic extracts of the plant on replication of human immunodeficiency virus-1 (HIV-1), simian immunodeficiency virus SIVmac251 and HIV-2 were determined. The results supported the remarkable antiviral activity of both fractions against all three viruses[59]. Moreover, the methanolic extract of *Euphorbia hirta* showed more efficacy than the aqueous extract.

In another study, the role of *Euphorbia hirta* against dengue was demonstrated. Dengue disease is a viral disease caused by four distinct serotypic members of the family Flaviviridae and genus Flavivirus, including DENV 1-4[60]. The *Euphorbia hirta* plant has been regarded as a game changer in dengue management. Clinical investigation of *Euphorbia hirta* has been recorded against age group 30 - 35, which after the supplementation revealed an approximately 70% reduction in flu-like symptoms caused by dengue[61]. The *in vitro* analysis of the ethanolic extract of the plant showed remarkable inhibition of plaque formation up to 85% and 34.7% against DENV-1 and DENV-2[62], respectively. Some of the studies that have been carried out for the calculation of the anti-dengue property of *Euphorbia hirta* are listed in **Table 3**.

Table 3: List of some of the research investigations performed on the anti-dengue potential of *E. hirta*

Study	Results	Experimental model	Plant part(s)/extract
Apostol *et al.* 2012	The administration of *E. hirta* continuously for 14 days to rat's exhibit enhancing effects on platelet count and reductive effects on clotting and bleeding time.	Rats induced thrombocytopenic by ethanol (i.p injection) (*In vivo* assay model)	Decoction of fresh whole plant
Arollado *et al.* 2013	The consecutive treatment of rats with *E. hirta* for 9 days increased mean platelet count by 80%.	Rats induced thrombocytopenic by Anagrelide (i.p injection) (*In vivo* assay model)	Water extract of leaves
Coloma *et al.* 2015	A surveillance study of questionnaire was executed in Agoo, La Union, Philippines demonstrated Tawa-Tawa is very high in demand against dengue. The thrombocytopenic rabbits fed with *E. hirta* juice showed remarkable increase in the platelet count with 24 h of time.	Descriptive ethnobotanical survey. Aspirin-induced thrombocytopenia rabbits (*In vivo* assay model)	Expressed juice of *E. hirta*. Expressed juice of *E. hirta*
de Guzman *et al.* 2016	The study showed very high percentage of women of 60-80 years of age have remarkable primary and secondary knowledge of using *E. hirta* against dengue.	Ethnopharmacological survey	Decoction of leaves or bark
Mir *et al.* 2012	Post 24 h of *E. hirta* administration over 70% patients showed promising platelet increase. Patients showed noticeable recovery in flu and fever like symptoms.	Clinical study, Sir Ganga Ram Hospital, Lahore using on admitted dengue patients.	Herbal water
Saptawati *et al.* 2017	Virus inhibition by 34.7%.	*In vitro* assay for DENV-2 serotype	Ethanol extract of leaves
Siva Ganesh *et al.* 2015	Quercetin molecule has been reported to possess extraordinary binding efficacy against dengue virus. The leaves of *E. hirta* are rich in quercetin and thus effective against dengue virus.	Molecular docking study using phytochemicals with 2P40-methyl transferase, and 2FOM-dengue proteases of dengue	Leaves

Continued on next page

Table 3 continued

Study	Results	Experimental model	Plant part(s)/extract
Tayone *et al.* 2014	Ethyl acetate fraction of dichloromethane and methanolic extracts of *E. hirta* inhibit the plaque formation by 85% in dengue virus serotype-1. The extract fraction resulted in the identification and isolation of Nine compounds.	*In vitro* assay	Ethyl acetate/methanol and ethyl acetate partitioning and tea of *E. hirta*.

Furthermore, *Euphorbia hirta* has been reported to have evident antiviral potency against herpes, coxsackie and polioviruses. *Euphorbia hirta* has also been reported to have selective antiviral activity against HSV-1 with an MIC value of 0.1 mg/ml[63]. The leaf extract of *Euphorbia hirta* plant has been reported to impart protective cover against potato virus X in both systemic and hypersensitive hosts. The active constituent actinomycin D was systemically sensitive toward the virus X[64].

POSSIBLE ROLE OF *EUPHORBIA HIRTA* AGAINST SARS-COV-2

Unfortunately, communicability and COVID-19 infection are growing rapidly each day, causing huge human and economic losses globally[65]. The common clinical symptoms identified among COVID-19 patients include cough, shortness of breath, fever, and respiratory symptoms (such as inflammation caused by allergy to the pathogen). *Euphorbia hirta* is an important medicinal plant involved in the global traditional medicine core, including Ayurvedic medicine and Traditional Chinese Medicine[66]. The lyophilized aqueous extract of *E. hirta* revealed potential antipyretic, anti-inflammatory and analgesic actions in xenografted mice and rat models. The antipyretic effects of *Euphorbia hirta* were evaluated via yeast-induced hyperthermia and showed potential activity at 100-400 mg/kg[67]. Furthermore, writhing and hot plate tests showed anti-analgesic activity in a dose-dependent manner at 20 mg/kg and 25 mg/kg, respectively. Additionally, strong anti-inflammatory activity of *E. hirta* was observed in carrageenan-induced edema test rats at 100 mg/kg[68]. A clinical study in dengue patients performed by S. D Pareera *et al.* at Sir Ganga Ram Hospital Lahore revealed that the administration of an aqueous extract of *E. hirta* orally enhanced the total leucocyte count and platelets in patients aged 30-55 years. Moreover, 70% of the patients showed a response of lowering flu symptoms and fever. Moreover, the ethanolic extract of *Euphorbia hirta* demonstrated significant inhibition of dengue virus stereotypes 1 and 2[69]. *Euphorbia hirta* is also known as an asthma plant and possesses remarkable activity against asthma[70]. Diarrhea is a key symptom commonly identified in COVID-19 patients. *Euphorbia hirta* plant has been used against several gastrointestinal disorders, including diarrhea and ulcers. The methanolic extract of *Euphorbia hirta* has been identified with rich flavonol glucoside content, including afzelin, myrcitrin and quercitin. The antimicrobial analysis of these compounds yielded IC_{50} values of 1.1, 5.4 and 4.1 against malarial parasites, respectively[51]. Furthermore, the plant *Euphorbia hirta* has been reported to have high free radical scavenging properties. The maximum DPPH scavenging activity was reported by leaves, followed by flowers, roots and stems ($72.96 \pm 0.78\%$, $52.45 \pm 0.66\%$, $48.59 \pm 0.97\%$, and $44.42 \pm 0.94\%$)[71]. Furthermore, *Euphorbia hirta* has been reported to induce potential nonspecific immune responses, such as phagocytic ratio and lysozyme activity, *in an Aeromonas hydrophila* pathogen-infected fish model[72]. At higher concentrations, the plant was successful in eliminating Aeromonas hydrophila from the kidney and blood and enhanced the numbers of WBCs, RBCs and hemoglobin in test fish. Additionally, *E. hirta* leaf extract enhanced the fabrication of $\log_2$ antibodies[73]. *Euphorbia hirta* also showed potential immunomodulatory effects against animal models. The maximum inhibition was recorded at 100 and 200 mg/kg, wherein it remarkably blocks the generation of cell-mediated immune responses (IL-2, TNF-α, IFN-γ, $CD3^+$, $CD4^+$ and $CD8^+$)[74].

SARS-CoV-2 attaches to the host cell using the receptor-binding domain (RBD) in its spike protein[75]. The RBD recognizes the ACE2 binding ridge on the outer cell membrane of the host cell, which leads to smooth entrance. The SARS-CoV-2 RBD bears an ACE2-binding ridge with a more compact conformation. Moreover, two virus-binding hotspots at the RBD–ACE2 interface are stabilized by several residue changes. The methanolic extract of *Euphorbia hirta* roots and leaves has been reported to possess substantial angiotensin converting enzyme (ACE) anti-dipsogenic and inhibition activities. The extract suppressed the activity of ACE 50% at 160 μg and 90% at 500 μg[76]. The possible inhibition of the interface between SARS-CoV-2 and human host cells is shown in **Figure 5**.

FUTURE PROSPECTS

It is essential and needed of this era to continue the expansion of drug development and therapeutics based on plants and their chemical composition. Drugs and therapeutics based on plants are economical (cost effective) and are believed to be less toxic than synthetics. Cancer is a global health problem, making it difficult for scientists and researchers to overcome this ailment. Plants have assisted humanity against several malignancies in the past, and they are believed to do so currently and in the future as well. There are several drugs based on plants that have been approved for cancer chemotherapy, such as Taxol and paclitaxel. *Euphorbia hirta* has a substantial potential to inhibit different cancers in humans due to its rich phytochemistry and active constituents. This plant

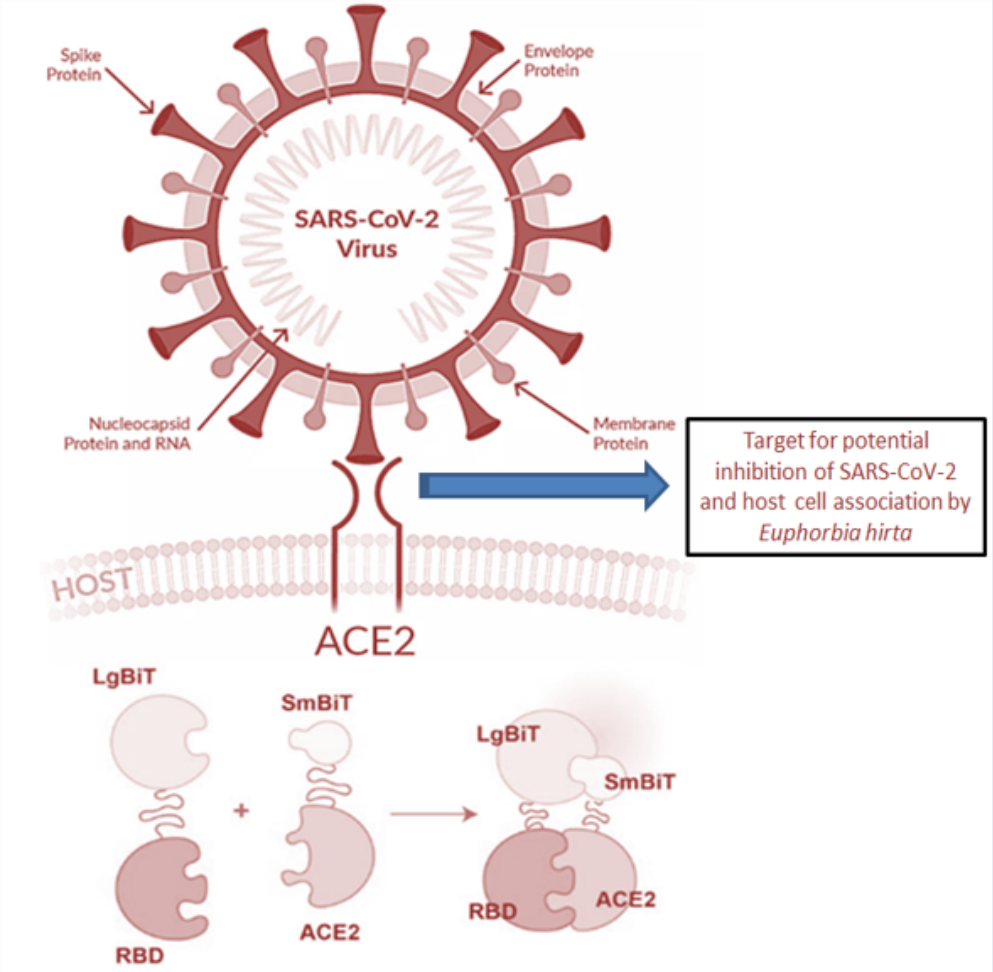

Figure 5: **Target site for possible inhibition of SARS-CoV-2 entrance to host human cells. Adapted from Brown *et al.* 2021 [77].**

bears a unique class of compounds called euphorbins, and they are complex in structure and active in nature. Therefore, it is believed to possess remarkable pharmacological potential, which needs to be explored.

It is highly recommended to push on progress in the field of potential antiviral therapeutics designed on natural products and their synthetic derivatives. Moreover, to look for therapeutics against coronaviruses, natural products have been the leading sources that have assisted human civilization in overcoming health hazards since the ages. The therapeutics designed on natural products have significant benefits over the synthetic ones, such as their cost effectiveness and miniscule or lack of side effects. Despite noteworthy developments in the field of vaccine development in this modern era, we lag behind in terms of developing breakthrough vaccines for several viruses, including SARS-CoV-2. Therefore, it seems to be a very difficult job to develop a potential treatment methodology for the management of such infectious viral diseases. However, plants such as *Euphorbia hirta* and their bioactive phytochemicals have tremendous potential to serve humanity in overcoming these infectious diseases. Based on docking studies and the antiviral properties of phytochemicals, *E. hirta* could also prove advantageous against coronaviruses. The rapid genomic mutations in SARS-CoV-2, HIV and HSV are the key drawbacks of antiviral therapeutics in targeting specific proteins and genes. The plant *Euphorbia hirta* has huge potential against COVID-19, as it showed against different viruses, such as malaria, HSV and dengue. The plant has a strong antiviral property and has significant potential to target key sites, enzymes and replication of SARS-COV-2. Therefore, we recommend clinical in-

vestigations of *Euphorbia hirta* against this lethal disease.

CONCLUSIONS

Euphorbia hirta is a valuable medicinal plant used globally in different traditional systems of medicines. It has been reported to have various bioactivities against a wide array of human disorders. Most importantly, the plant as a whole bears a huge variety of chemical entities that enhance its therapeutic potential. The plant as a whole has been shown to have remarkable antiviral potential against HIV, DANV, HSV, etc. and enhancing immune responses against pathogens. It has great potency for free radical scavenging and ACE inhibition. Therefore, these features of *Euphorbia hirta* may play an advantageous role throughout the management of highly infectious and deadly viral diseases such as COVID-19.

ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus-2, **ACE**: Angiotensin-converting enzyme, **ABTS**: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid, **CD**: Cluster of differentiation, **COVID-19:** Corona Virus Disease 2019, **DPPH**: 2,2-diphenyl-1-picrylhydrazyl, **DENV**: Dengue Virus, **HSV**: Herpes Simplex Virus, **HIV**: Human Immunodeficiency Virus, **IL-2**: Interleukin-2, **IFN-γ**: Interferon gamma, **MIC**: Minimum inhibitory concentration, **RBC**: Red Blood cells, **RBD**: Receptor Binding Domain, **WBC**: White Blood Cells, **TCM**: Traditional Chinese Medicine, **TNF-α**: Tumor Necrosis Factor Alpha

ACKNOWLEDGMENTS

Aadil Khursheed is highly thankful to Dr. Vikrant Jain and the whole Department of Chemistry, Madhyanchal Professional University, for providing academic guidance and platform.

AUTHOR'S CONTRIBUTIONS

All authors equally contributed to this work, read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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