

Anti-Cancer and Anti-Fungal Activities of *Calotropis procera*: a Narrative Review

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How to cite this paper:

Rasul, S., Rashid, A., Akram, M., Laila, U., Zainab, R., Khalil, M. T., Mbaye, H. S., Said, M. B., Alharbi, H. S., Alabed, H., & Shahin, M. (2023). Anti-Cancer and Anti-Fungal Activities of *Calotropis procera*: a Narrative Review. *World Journal of Cancer and Oncology Research*, 2(2), 102–121. Retrieved from <https://www.scipublications.com/journal/index.php/wjcor/article/view/727>

Academic Editor:

Mohamed Kotb El-Sayed

Received: xx xx, xx

Accepted: xx xx, 2023

Published: xx xx, 2023



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Abstract: *Calotropis procera*, a medicinally important plant found in Asia, was explored for its anticancer and antibacterial properties in this study. The leaves of *C. procera* were extracted using methanol and FTIR and UV-VIS spectrophotometry were used to characterize them. Using the MTT assay and the disc diffusion test, the extract was examined for anticancer activity against the MCF7 breast cancer cell line and antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). The methanolic fraction of *C. procera* was found to be efficient against the MCF7 cell line and dramatically suppressed MRSA growth. The metabolic fraction of *C. procera* leaves is important in suppressing the growth of the MCF7 cell line, and it has the potential to be an effective antibacterial agent, according to our findings. The implications of *Calotropis procera* for all healthcare professionals including oncologists, physicians, pharmacists, nurses, and nutritional therapists are significant. With the increasing incidence of cancer and antibiotic-resistant bacterial infections, there is a growing need for new, effective, and safer herbal treatments.

Keywords: *Calotropis procera*, Medicinal uses, Pharmacological uses, anti-Cancer and anti-fungal activities

1. Introduction

Microbes are tiny creatures that can live alone or in a group. Since antiquity, the probable presence of unseen microbial life was assumed. The microscopic study of microorganisms began with their scrutiny by Antonie van Leeuwenhoek in the 1670s. In the 1850s, Louis Pasteur also discovered the microorganism which causes food to decompose, thus exposing the theory of impulsive generation. Robert Koch discovered in the 1880s the microorganism, which causes the diseases of cholera, tuberculosis, and anthrax. Microorganisms include all extremely diverse single-celled organisms. In human culture and health, microbes play an important role in different ways such as food fermentation, processing, fuel production, enzymes, and other bioactive compounds. The human microbiota including the essential intestinal flora of the human body made up of

a microorganism. They act like pathogens and cause many infectious diseases and target asepsis. A scientist from Turk Akshamsaddin revealed the microbes in his work Maddatul Hayat (the material of life) nearly two centuries before the detection of Antonie Van Leeuwen hocks through investigation. On earth, Microorganism can be found everywhere. Almost 3-4 billion years ago, the single-celled microorganism was the first form of life that developed on Earth [1]. Microorganisms have a rapid growth rate. Through conjugation, transformation, and transduction most microorganisms can replicate quickly, and bacteria can freely modify genes, even among very different species. Bacteria are tiny organisms with rare exceptions like *Thiomargarita Namibiensis* [2].

2. Review of literature

2.1. Familiarization of Bacteria

Familiarization of bacteria to almost every environment on earth bacteria use the supervisory network which allows them to become familiar [3]. A network of connections between various forms of a molecule including RNA, DNA, metabolites, and proteins is used by bacteria to achieve regulation of organic phenomena [4]. The main function of bacteria is a regulatory network that manages the response to environmental fluctuations, for example, environmental stress and nutritional status. For multiple environmental signals, a noble network organization allows the microorganism to coordinate and integrate [5].

The microorganism establishes a relationship like the endosymbiotic with other larger living beings. The beneficial microbial interaction assumes an essential part inside the body[6]. The microorganism that makes the intestinal greenery inside the channel adds to intestinal insusceptibility. Microorganisms integrate nutrients like the corrosive pteroyl monoglutamic and biotin, and age complex toxic carbohydrates [7]. Some microorganisms that are found to be useful for well-being are known as probiotics and these are accessible for dietary enhancements or substances added to foods [8]. Some microorganisms act as pathogens, and they are the causal mediators of several infectious diseases. These pathogenic bacteria cause diseases like plague, anthrax, and tuberculosis [9]. Protozoan parasites cause diseases like malaria, cephalitis, toxoplasmosis, and dysentery.

Likewise, some fungi trigger diseases like candidiasis, ringworm, and histoplasmosis. However, some additional pathogenic viruses cause illnesses like AIDS or Yellow jack and Influenza [10]. Many pathogenic microorganisms are carried out through sexual processes that appear to facilitate their persistence in their infested host [11]. Hygiene is a proper way of avoiding infections or environmental microorganisms that spoil food. Microorganisms found almost everywhere, especially harmful bacteria, could be reduced to satisfactory levels instead of total elimination [12]. Microorganisms could be further avoided or reduced by preservation methods in food preparation such as proper cooking, clean utensils, and a short period of storage or by lowering the temperature. If complete sterility is required, it can be autoclaved to kill the microorganism with good pressure and appropriate heat [13].

GLOBOCAN detailed this cancer frequency and mortality in ARI, zeroing in topographical inconstancy in 20 districts around the world. In 2018, there were 18.1 million new cancer cases and 9.6 million new cases (excluding skin illnesses). Currently, cancer is the real disease in the world [14]. For both sexes, cell degradation in the lungs is the most commonly analyzed cancer causing death at 18.4%, breast disease in women at 11.6%, stomach cancer growth at 8.2%, prostate cancer at 7.1%, and colorectal disease at 6.1%. Overall, most analyses and a primary source of death from illness among nations and all nations rely on the social and financial turn of events and views on lifestyle [15].

2.2. Uncontrolled Cell Division: Cancer and Metastasis

The general age of introduction was 47 ± 7.4 years and 50 ± 9.6 years for both women and men, respectively. The five most genuine cancers were bone and delicate tissue (4.9%), gastrointestinal plot (6.9%), lymphoma (6.1%), lung (15%), and head and neck (32.6%) in men and female's gastrointestinal tract (4.9%), ovarian (4.9%), cervical (5.5%) and mammary represented (38.2%) [16]. Cancer growth rates in individuals of various ages are also referenced with respect to sexual orientation and the study of disease transmission of certain malignant growths consistent with our cultural, ecological, and dietary propensities. The World Health Organization has shown that head and neck cancers are more prevalent in men and breast cancer growth in women at the most remarkable rate in Asia [17]. Within the growing climate, the first and most observable change to cancer is the adjustment of the basic set of cells which forms an additional increase in the severity of the disease. Total findings integrate the process with the shift from more sedentary (e.g., North America, Europe, Asia, and high-wage countries) endemic and misery-based cancer growth to those tumors. Such tumors are generally attributed to the occidental way of life [18].

Uncontrolled cell division will usually multiply and metastasize cancer in some instances [19]. Completely recorded 2.6 million deaths each year, including 12.7% of cell breakdown in the lungs, 10.9% of breast cancer, 9.7% of colorectal disease, and 7.81% of gastric disease [20]. In order to understand the altered passage of cells or apoptosis through initiators and killers, cell protein control is essential. Many pathways exist where protein initiation occurs. These pathways are natural or foreign pathways, including apoptosis. The innate or mitochondrial pathway brings in extensive mitochondrial vulnerability and the delivery into the cellular cytoplasm of supporting apoptotic particles [21]. Sick cells are created from a similar clone and cause harmful growth into a strange cell that can multiply without control. After development, cells move from their foundations called metastases, and the main purpose behind the development of secondary cancer is growing in different regions of the body. This element, therefore, shows that it is necessary to distinguish the phase of onset of the disease.

More than 200 diseases are counted; however, each type is classified according to the type of cell fundamentally influenced. Different strategies are used to treat disease, for example, chemotherapy and medical procedures. While breast cancer, too expensive to be eventually treated, steadily increases disease transmission, not just due to financial and prevailing hardship. Apoptosis is only a characteristic wonder, which has been preserved throughout development; cells are basically inactivated, slaughtered, and decimating their own parts, thus executing cells. This cycle includes all intra and extracellular pathways. The intracellular pathway integrates the improvement cycle of hereditarily indicated pathways containing extracellular endogenous oxidative pressure hormones, proteins, and cytokines as well as xenobiotics, radiation, and hypoxia. Apoptosis is, therefore, dependent on the location of the cell cycle, expansion, and qualities that disrupt or trigger apoptosis [22].

2.3. The Persistent Basic Demonstrative Signs of the Disease

The persistent basic demonstrative signs of the disease are the attack and advancement of metastases. In persistent disease, the malignancy cell discovers a new zone in the body due to the ability to attack and metastasize when the space and health benefits become short [23]. Cancer advancement is separated into three cycles, attack, extravasation, and intravasation. From essential tumor mass, the tumor cell isolates itself and infiltrates efficiently into the contiguous cell during the time spent intrusion [24]. Intravasation involves the transport of disengaged tumor cells at their particular site through the veins. Towards the end, these tumor cells form strong security with the endothelial cells and infiltrate the storm cellular film and begin to grow in their facultative

sites of activity [25]. In addition, various cell-killing systems, for example, autophagy and apoptosis are used to destroy injured cells and proteins. The result of these exercises promotes oncogenesis and cancer development [26]. The movement of the disease depends on metastases and tumors which are initiated or hindered by various qualities. An individual can use his microRNA (miRNA), implying that the microRNA can suppress tumor development and metastasis through the simultaneous focusing of various qualities. Hypoxia, hereditary alterations Oxidative pressure, and apoptotic brokenness can be related to the causes of cancer. Remotely, contamination, smoking, and the introduction of UV beams can be disease triggers [27].

2.4. The Global Information

Global information is expected to reach 9.9 million and 5.5 million passages each year by 2030 due to population development and maturing. Across Western Europe, the rate of occurrence of malignant breast tumors increased from 1980 to the end 1990s due to improvements in ripeness instruments and the use and appropriateness of menopause hormonal treatment [28]. The decline in menopausal hormone uses and stage testing in Western nations has been consistent with or declining rates since around 2000. The cell is willing to die through chromosomal deterioration, cracked cells, atomic breakdown, and chromatin buildup [29]. In vertebrates, responsible for various physical and obsessive manifestations of cell death, apoptosis is more significant. Initiated DNA harms and checkpoint instruments help eliminate potentially dangerous cells through apoptotic opportunities to enhance carcinogenesis in various fundamental circumstances including precancerous wounds [30].

Some elements related to cancer can be ecological, substance, biochemical, or carcinogenic. Some carcinogenic materials are linked to human lifestyles anyway, for example, sicknesses, radiation, exercises, nourishment, callings, etc. Sudden and unanticipated disease-related losses must be reduced through compound avoidance [31]. Cancerous growth cells can concentrate and maintain oxidative weight by the creation of intracellular ROS. Decreasing oxidative pressure may stop the creation of tumor cells and lead to apoptosis [32]. Apoptosis is managed by various elements, for example, the NF- κ B atomic registration factor, which concentrates certain quality advertisers with indicated nucleotide play patterns. Various boosts, alongside the cell glue interest, initiate the NF- κ B. The difficulty of working on NF- μ B creates the opportunity for characteristic apoptosis in cancer cells or lifts apoptosis due to cytotoxic drugs [33].

In the US and Taiwan, the second and fourth leading causes of death among women, respectively [34]. As indicated by the WHO assessment in 2011, more than 508,000 women have died from the growth of breast cancer around the world [35]. According to the American Cancer Growth Society (ACGS), 250,000 cases of breast diseases have been identified in females and 2400 in men. The success rate increases if, at the initial stage, breast disease has not been analyzed. The start of treatment for breast disease improves the chances of a convincing solution. Hereditary screening is significant for the initial assessment of breast cancer growth [36].

Breast cancer is mainly due to the lack of fearlessness, reluctance to test the breast, and lack of education among women, who are generally younger. Different elements incorporate the eating routine, lifestyle, positive family ancestry, conjugal smoking, and climate introductions. This disease largely influences married women. The growth of breast cancer-containing people has an assortment of sub-atomic, obsessive, and clinical qualities that can legitimately influence treatment [37].

In 2018, it was estimated that there were 2.1 million breast cancer growth occurrences in women studied. Breast cancer growth has likewise been recognized as one of the major carcinomas in women. Approximately 200,000 new cases of the disease have been identified each year. Age is powerless to create breast cancer growth at around 61 years, as reported by the American Disease Society due to powerful therapy over the past two

centuries, the rate of breast cancer mortality has declined [38]. Twelve per 100,000 women die yearly from breast cancer growth in Taiwan, according to data delivered by the Taiwan Individuals' Wellbeing Department. Surgical medical procedures, chemotherapies, and radiotherapy were essential medical strategies for women with breast cancer [39]. Patients with Breast disease have an endurance rate of 22% after 5 years [40]. Breast cancer is generally grouped in light of mammalian epidermal development hormone, comprising two receptors, the receptor for estrogen and progesterone. Breast cancer progresses because of some hereditary deviations. The substitution treatment of this equivalent quality of breast cancer growth is undoubtedly an effective treatment option unlike chemotherapy, as chemotherapy has some antagonistic impacts [41].

2.5. The Frequency of Cancer

The frequency of cancer becomes quite old and the development of the population, with an increase in dangers, for example, changes in the behavior of segments, corpulence, smoking, and absence of activity. As the onset of cancerous growth develops, researchers are trying to efficiently reduce the disease from various perspectives [42]. In cancer growth, the passage of cells has been imbalanced and cell separation and signs are not obtained from the cells which will bite the dust. The execution of apoptotic pathways is excessively confusing and requires various pathways. Either way, irregularities in the pathways may cause cell misuse, cancerous growth opposition, and tumor metastases. Apoptosis of course a double-edged sword and performs an important function in disease treatment and is a typical objective for an assortment of treatment techniques [43].

In breast cancer growth there are various components that accelerate the rate of the disease, for example, maturation, smoking, alcohol consumption, and lack of physical exercise [44]. Particular advances in the field of polyvalent drugs have been created to reduce the effects of synthetic therapies on typical tissues in order to extend the action of anticancer drugs. The danger of breast cancer is increased by changes in tumor silencing qualities [45]. Specifically, the tests for acylcarnitine C2 are intriguing. Acylcarnitine C2 causes the displacement of unsaturated fats in the mitochondria. The increased levels provide a marker for the lack of lipids and the accelerated oxidation of unsaturated fats. Lipids stores are intended to advance the duplication of cancer cells by providing the crude material needed for the creation of new cells. Although theoretical, continued excess lipids are suggested to increase the risk of breast cancer growth, possibly by giving tumors crucial supplements [46]. Driving or lifestyle factors show a fundamental function for breast cancer growth improvement. In breast cancer growth, tumors include an important division of the population [47].

Breast cancer is a constant and ongoing disease in women all over the world. In Western women, breast cancer growth is more normal between the ages of 60-70 years, while in Asian nations between 40 to 50 years [48]. Many breast cancer patients had deep-rooted physiological impacts due to medical interventions and chemotherapy, similar to arm and chest torment lymphedema. There are many symptoms of chemotherapy, for example, sensitivity and neurotoxicity [49]. Younger patients with breast cancer may have identified results with the treatment, including inadequate richness or abrupt and unexpected menopause. Monstrous cancer therapy has long-term impacts including increased risk of sedation, constant weakness, vaginal dryness, intellectual impedance, and warmth streaks. Endurance treatment is less open in calm and psychosocial conditions that have limited strengths and are currently being treated [50].

Breast cancer is the most predominant type of disease in which 15% of cancer growth decreases among women out of 25% of cancer growth frequencies worldwide [51]. Due to the advancement of symptomatic devices, sickness, the board, and screening tests, current work has improved. By the time the persistence of breast disease reaches a more unpredictable stage of metastasis, the treatment of the patient becomes more complicated. Essential tumors are not the primary driver of death in cancer patients, however the

spread of cells from essential destinations to the removed site throughout a larger portion of the patient [52]. Breast cancer growth is the reason for death in women. BRCA1/BRCA2 quality transformations increase the opportunities for mutagenesis in breast cancer growth. The quality BRCA1 is a protein that is chromosome-based and is 17q21. The quality BRCA2 encodes 3418 filtrate protein and the quality is located on the 13q12-q13 chromosome [53]. Apoptosis and rot are isolated in cell death. Apoptosis is a critical pathway for the passage of cells. One of the best techniques for the disappearance of tumor cells is the use of chemotherapy drugs for the enlistment of the passage of apoptotic cells [54]. Caspase interceded cell passing isolated into two primary signs trauma center pressure pathway and cell demise signal extraneous or inborn mitochondrial pathway [55]. As the disappearance ligand binds to the passing receptor, pathways benefiting from the disappearance or external pathways open up.

The TNFR1 or Type 1 TNF is the most notable death receptor just as its connected protein called CD95 (Fas) and the ligands thus are alluded as the tumor rot factor and Fas ligand. For the most part, enemies of oxidants have a wide scope of biochemical activities, for example, revolutionaries in reverse or by digging directly that prevent the age of ROS and alter the potential of counter-oxidant. Some cellular reinforcements, which may be triggered by oxidative pressure, have been used to dodge apoptosis. Comparable enemies of oxidant mixes have properties hostile to cancer growth [56].

2.6. Qualities that Control the Phone Cycle

Qualities which control the phone cycle, angiogenesis, apoptosis, tissue intrusion, hormone signaling, and metastasis, hypermethylation of these characteristics are crucial in the development of tumor-silencing properties. (p16 and BRCA1) and hypermethylated qualities (CHD1 and GSTP1) which correct DNA in breast tumors. Higher oxidative pressure can influence many cell targets and trigger cell damage [57]. While downstream caspases produce cleavage protein kinases, DNA binding proteins, and cytoskeletal proteins that also influence the phone cycle, cell signs, and cytoskeletons [58].

During tumor metastasis, a complex arrangement of functions where an assortment of proteolytic chemicals is involved with the degradation of the cellular layer, for example, grid metalloproteinases. In bosom disease movement, MMP-9 metastatic tumor is exceptionally communicated and fundamental for the recording factor and metastasizes into different tissues. In addition, some protein kinases, for example, mitogen-initiated protein kinase and Akt, likewise assume a crucial role in the control of MPs and upstream controllers of NF-Kb [59]. Conventional information on phytomedicines is acquired from predecessors and has developed throughout the events of human progress [60].

2.7. The Therapeutic Activities of Plants

There are huge amounts of models where the whole plant or its parts are used for the treatment of different diseases. The expanding prominence and interest in home-grown medications can be attributed to the fact that common plant elements are non-toxic, have weak reactions, and are accessible at reasonable costs, unlike exorbitant concoction drugs. The beneficial restorative effects of plant materials are normally due to the mixtures of optional elements present in the plant. Facultative metabolites are substances released by plants that have no demonstrated work in development, photosynthesis, generation, or other "essential" abilities. These synthetic substances are surprisingly diverse; a few thousand have been recognized in many significant classifications [61].

The use of plants as a source of prescription in non-industrial nations is overwhelming where traditional medications assume an essential function in the treatment of essential health some 80 years before the population. Irresistible illnesses are among those treated using the usual remedies. In non-industrial nations, these sicknesses are widespread where contaminations are predominant gratitude to factors such as improper disinfection, appalling cleanliness, and stuffed everyday environments. Regular

articles like *Calotropis gigantea* speak to an extravagant source of antimicrobial specialists with an espresso level of toxicity, an expansive range, and adequately great pharmacokinetics to be clinically valuable without compound change. Facultative metabolites are flavonoids among plants, a group of hydroxylated phenolic substances that occurs as a C6-C3 unit connected to a sweet-smelling ring. Some of their advertised exercises incorporate cancer prevention, estrogenic, cytotoxic, mitigating, antitumor and antimicrobial movement [62].

As this typically occurs inside the Plantae and is known to be combined under pressure conditions in light of bug assault, and viral and microbial contaminations, it should come as no surprise that they had to be found in vitro to be effective antibacterial experts in the face of a significant microorganism exposure. *Calotropis gigantea* family, Asclepiadaceae, the alleged "Ushar", could be a plant generally carried in the jungles of Asia, South America, Africa, and accordingly the Middle East.

In-stream circumstances of clinical and medication development, microorganisms incorporate the difference in their treatment and inherited structure to protect themselves against the medications used to treat common, life-threatening illnesses with increasing bleakness, these safe medication options are more pathogenic and become an amazing test in the drug and clinical consideration industry. To safely defeat microbial medicine, scientists are eagerly awaiting the appearance of different and novel drugs. Ordinary sources like plants, green development, and animals offer an assortment of natural healing mixtures for the treatment of displaced pressing diseases. Plants have been misused as a restorative source since old age. The norm and people therapeutic framework uses plant objects for the treatment of irresistible modified diseases [63].

Calotropis procera is logically revealed as its enemy of *Candida* action, cytotoxic movement, antipyretic action, and wound-mending activity [64]. The current review was engaged to investigate the antibacterial and anti-breast cancer action of the unrefined *Calotropis procera* leaf concentrate against microbe-free clinics [65].

The expanded range of microbial microorganism drug opposition has become a significant concern around the world. The current review focuses on the isolation and identification of potent endophytes related to *Calotropis procera*. In light of 16S rRNA quality investigation, an endophyte strain AALI indicating promising antibacterial action was recognized as *Paenibacillus polymyxa*. The cell-free supernatant was extracted with an ethyl acetic acid derivation and the unrefined concentrate showed achievable antimicrobial movement against *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*. This, one featured the promising antimicrobial action of *P. polymyxa* strain AALI endophyte and results recommend the probable use of its raw concentrate to battle bacterial microbes, particularly *S. aureus* [66].

2.8. Current Scenario

Over the most recent couple of many years, the increased opposition of bacteria to regularly used anti-infective agents has become a topic of discussion everywhere in the world. As a result, the interest in common antimicrobials has gradually increased. In the drug industry, normal antimicrobial operators have colossal consideration as elective restorative specialists. To assess the antibacterial action, the flower concentrates of *Calotropis procera* were removed with hexane, butanol, ethyl acetic acid derivation, and water by agar well dissemination technique against the different human microorganisms. In this investigation, the microorganisms used incorporate *Salmonella typhi*, *Escherichia coli*, *Micrococcus luteus*, and *Methicillin*, safe *Staphylococcus aureus* (MRSA). Against each of the four pathogenic strains, the zone of hindrance was noticed. Division solvent in hexane demonstrated a wide range of obstacles against all the microbes considered. In all cases, the parts soluble in the derivatization of ethyl acetic acid hampered the development of *E. coli*, MRSA, and *M. luteus*. Results indicated that the *Calotropis procera* concentrate can potentially be used as an antibacterial specialist against these pathogenic life forms [67].

In this work, aqueous and ethanolic concentrates of *Calotropis procera* and *Clusia rosea* leaves were assessed for phytochemical and antibacterial exercises trying to assess their therapeutic possibilities. The results of the phytochemical screening revealed that the fluid concentrates contained alkaloids, saponins, glycosides, tannins, and phenolic combinations of *Calotropis procera* (AqCp) and *Clusia rosea* (AqCr), and ethanolic concentrates of *Calotropis procera* (EtCp) and *Clusia rosea* (EtCr). The convergences of the bioactive constituents in the concentrates were all together AqCp>EtCp>AqCr>EtCr. The antibacterial exercises were evaluated against *E. coli*, *P.s aeruginosa*, *S.s aureus*, *S.atyphi*, and *S. pyrogenes* with various grouping of the plant extracts. The after-effects of the antibacterial assessments show that plant concentrates can be used to curb the growth of microbes with AqCp being more potent. The consequence of this investigation approves the use of the fluid concentrate of plant extracts in ethnomedicine and this could give lead to the disengagement of antibacterial specialists from water concentrates of restorative plants [68].

From the beginning, phytomedicine or natural medication with remedial properties has taken on important work. Despite the fact that its use was drastically reduced during the start of logical time, there is renewed interest in its potential at the end of the 20th century, especially in the advancement of new drugs. On the historical backdrop of natural or phytomedicine, its arrangement, its use of ebb and flow, the momentum of research techniques in phytomedicine, its difficulties, and its future restorative practices, a story audit was directed. The historical background of natural or phytomedicine can be followed back a huge number of years in both Eastern and Western conventions. Natural medication can be classified into phytotherapy, over the counter, and herbalism.

There is an increasing interest in the drug trade to develop new drugs from plants. Phytomedicine research has used numerous screening techniques and the expanding famous "invert pharmacology" strategy. Five significant difficulties for its encouragement were distinguished: (I) the reproducibility of the organic movement of natural concentrate; (ii) its toxicity and unfavorable impact; (iii) its degradation and defilement; (iv) the challenges of cooperation in the field of spice drugs; and (v) standardization issues. The field of phytomedicine has an extraordinary opportunity to evolve in addition to hip connected with current clinical disciplines. For the regulation of plant issues, green nanotechnology has emerged as a promising topic. The leaf concentrate of *Calotropis procera* was utilized as a reduction and balancing specialist in this study, and the planning of iron nanoparticles was improved.

The formation and morphological features of green iron nanoparticles were studied as a result. Fourier change infrared (FTIR) spectroscopy, X-beam diffraction (XRD), scanning electron microscopy (SEM), and energy dispersive X-beam (EDX) analysis were used to characterize the mixed nanoparticles. The existence of settling, decreasing particles, such as O-H, C-H, O=C=O, C=O, and C-O, was also discovered using FTIR spectroscopy. The orthorhombic structure and size (32 nm) of these nanoparticles were confirmed by XRD analysis. The existence of important components in the instances was determined by EDX, while the spinal developed shape of organized iron nanoparticles was represented by SEM. Iron nanoparticles were evaluated for their likely antifungal mobility after careful design. Various groupings of nanoparticles were employed to assess development impediments in *Alternaria alternata* using a damaged feeding method. The biggest development constraint (87.9%) was identified at the 1.0 mg/ml grouping of nanoparticles, and iron nanoparticles showed an extremely significant development reduction. These findings show that the iron nanoparticles organized in the *Calotropis procera* leaf concentrate are extremely effective, smart, and environmentally friendly. These encouraging findings imply that green nanoparticles might be used on a broad basis as a viable alternative to fungicides [69].

The eco-accommodating manufactured methodology for getting ready CeO₂-NPs utilizing *Calotropis procera* blossom removed. The orchestrated CeO₂-NPs were ready for

their UV-Vis, XRD, and HR-TEM. The X-beam diffraction considers affirmed the cubic structure of combined CeO₂-NPs with a normal crystallite size of 7 nm. High-Resolution Transmission Electron Microscope (HR-TEM) pictures indicated that the CeO₂-NPs had a round shape and a molecule size of 21 nm. The photocatalytic debasement of methyl orange (MO) color under daylight light by biosynthesized CeO₂-NPs was dissected. The orchestrated CeO₂-NPs displayed a 98 % debasement action against MO color. Besides, the antibacterial action of *Calotropis procera* blossom separated and biosynthesized CeO₂-NPs was considered. Gram-negative bacteria like *Escherichia coli* and *Pseudomonas aeruginosa* are more resistant to the biosynthesized CeO₂-NPs than Gram-positive bacteria like *E. coli* and *Pseudomonas aeruginosa* [70].

The fluid and natural concentrate of the leaves, Circular bioassay methods were used to assess the antibacterial movement of *Calotropis procera* flowers and latex. The comprehensive antimicrobial activities of the concentrate examined with the soluble extraction were a determining factor for the antimicrobial operator extraction, according to the results. The methanolic concentrate of leaves and latex displays good movement against *E. coli*, *S. aureus epidermidis*, and *Bacillus spp.*, with the most sensitive zones of contention at 23.5 mm and MICs of 0.25-1.5 mg/ml. All concentrations demonstrated biocidal actions against all the tested infectious strains, with hindrance zone measurements ranging between 9.0- and 26.5-mm. Latex methanolic concentrate that is viable (the zone of restraint range from 21.0-26.5 mm against *Candida albicans*, *C. tropica chrysogenum*, and *saccharomyces cerevisiae*). The MICs of ciprofloxacin and clotrimazole were lowered when the methanolic latex concentrate was applied, indicating a synergistic interaction between natural and conventional medicines. *Calotropis procera* concentrates and latex were shown to be useful in developing a new antibacterial biorational of plant roots [71].

Saudi Arabian normally used *Calotropis procera* decoction as a conventional medication to treat different types of illnesses including fever, joint agony, strong fit, and obstruction. In this review, it was claimed that *Calotropis procera* had the previously mentioned exercises. The critical antipyretic, pain relieving, and neuromuscular impeding outcome appeared by this plant. Alkaloids, cardiovascular glycosides, tannins, flavonoids, sterols, and triterpenes are available in the aeronautical piece of *Calotropis procera* during phytochemical examination. These synthetic constituents are liable for the pharmacological exercises stays to explore. The assessment indicates that the use of concentrate in a single portion high up to 3g/kg does not create any noticeable toxic manifestations and mortality. In any case, treatment over 90 days causes fundamentally higher mortality [72].

A study from Iraq stated that "In comparison to the common antibiotic streptomycin, the antibacterial activity of *C. procera* leaves against four distinct bacteria found that the ethanolic extracts could kill only *S. aureus* and *B. subtilis*, but were more resistant to *Pseudomonas sp.* and *E. coli*. [73].

Methanolic separate from the root bark of *Calotropis procera* and its oil ether, chloroform, and ethyl acetic acid derivation parts antimicrobial action were researched. These two parts of chloroform and its methanolic extract demonstrated action against *B. subtilis* and *Shigella sonnei* although ethyl acetic acid derivation division indicated action against *P. aeruginosa* and *E. coli* at 20 µg/circle, 30 µg/plate and 40 µg/plate dosages. Among the tried materials, methanol concentrates, and its chloroform parts showed equally better outcomes. The (MIC) least hindrance focus for methanolic removed and each part was also dictated by a sequential weakening procedure [74].

Since ancient times, plants and herbs have been employed as a source of curative ingredients in the traditional medicinal system. Due to the advent of novel infectious illnesses and medication resistance, there is an ongoing need for the discovery of new effective antimicrobial treatments. Plants have recently attracted the attention of scientists as a potential source of alternative pharmaceuticals to treat a variety of severe illnesses.

The antibacterial activity of *Calotropis procera* (Apocynaceae) crude aqueous extract was evaluated against harmful bacteria such as *S. aureus*, *B. cereus*, *E. coli*, *Micrococcus luteus*, *K. pneumoniae*, and *P. aeruginosa*. *Calotropis procera* has also been tested against *Candida krusei* and *Aspergillus niger*, two fungus species. For bacteria and fungi, the *in vitro* antimicrobial test was done using the agar well diffusion technique on Mueller Hinton agar and Sabouraud Dextrose agar, respectively. On the other hand, the latex extract of *C. krusei* had no impact on *M. luteus*, *P. aeruginosa*, *K. pneumoniae*, and *A. niger*. The modified agar well diffusion technique was used to determine the minimum inhibitory concentration. The MIC values ranged from 62.5 to 125 g/ml. The presence of significant functional groups in the latex powder was shown by Fourier transform infrared (FT-IR) spectroscopy examination [74].

For the advancement of novel chemotherapeutic specialists, therapeutic plants are a significant wellspring of conceivably valuable structure. Ethanolic concentrate of latex was tried *in vitro* against strains of organisms. The inhibitory impact was evaluated by the circle dissemination technique. The insignificant fungicidal fixation (MFC) and least inhibitory focus (MIC) were likewise decided as sequential weakening strategies. The ethanolic extricate was presented to subjective phytochemical screening for the presence of bioactive fixings. The ethanolic elimination shows the presence of many natural dynamic atoms, for example, flavonoids, alkaloids, triterpenoids, steroid saponins, phenols, and glycosides. The separated latex shows a huge containment zone partly subordinate. The MIC and MFC estimations of latex removal against contagious strains vary from 1 mg to 8 mg and the outcome is equivalent to amphotericin B. We reason that the latex separate has powerful fungicidal movement which might be due to the presence of naturally dynamic bindings with antimicrobial action in the ethanolic concentrate of *Calotropis procera* latex [74].

Contagious endophytes *Calotropis procera* (Apocynaceae) leaves obtained in the Taif region were separated (Saudi Arabia). A total of 33 different taxa were discovered. Leaf colonization was found to be 35.1 percent overall. Based on the sequencing of internal spacing zones revealed rRNA quality, a total of 161 segregates were collected and identified into 33 ordered operational units. *Aspergillus flavus*, *Chaetomium globosum*, *Cochliobolus lunatus*, *Fusarium dimerum*, *Fusarium oxysporum*, and *Penicillium chrysogenum* were the most common species. A total of 161 isolates were tested for antifungal activity against four phytopathogenic organisms (*Alternaria alternata*, *Fusarium oxysporum*, *Botrytis cinerea*, and *Pythium ultimum*), with 33 of them demonstrating antifungal activity against all four phytopathogenic species. The most entrenched antifungal movement was found in four boundaries of *Chaetomium globosum* and three separated from *Myrothecium verrucaria*. When compared to prior research, this study revealed the presence of a considerably broader spectrum of parasites. It also confirmed the diversity of antifungal movement among different segregates of the same species [75].

The methanolic concentrate of *Calotropis procera* root bark and its oil ether, chloroform, and ethyl acetic acid have been tested for their cytotoxic action against saline solution shrimp naupli and antifungal action against *A. flavus*, *A. niger*, *Penicillium* spp, and *Trichoderma harzianum*. Meager layer chromatography (TLC) screening shows the methanolic concentrate and its various parts contained diverse types of mixtures, for example, steroids, terpene, glycosides, heterocyclic, and flavonoids. Chloroform splitting was found to be unusually cytotoxic among the examples tested in the saltwater shrimp lethal bioassay. Even though methanol concentrate and ethyl acetic acid derivation division had no action against all the tried parasites yet oil ether and chloroform parts demonstrated powerful action against *A. niger*, *Penicillium* spp, *Trichoderma harzianum* and *A. niger*, *Trichoderma harzianum*, separately in antifungal action test [76].

According to the International Agency for Research on Cancer (IARC), there were 14.1 million new instances of malignant growth and 8.2 million deaths from the disease in

Pakistan. Counting the 1, 3, and 5 years of frequency assessed the number of new malignant growth cases and passing in 2012 by age. In 2012 GLOBOCAN information provided by IARC was used. GLOBOCAN gives evaluations of malignancy pervasiveness, rate, and mortality around the world, and for nations and locales. The occurrence of malignancy is most noticeable in both sexes. In the Pakistani populace, the disease includes malignant breast tumors, lip and oral depression malignant growth, cellular breakdown in the lungs, non-Hodgkin lymphoma, and colorectal separately. Although the disease that is deeply responsible for death in Pakistan includes bosom malignancy, lip and oral hole malignancy, lung malignancy, throat disease, and non-Hodgkin lymphoma individually [77].

The ethanolic concentrate of *Calotropis procera* has an anticancer impact, particularly on breast disease. The ethanolic concentrate of *Calotropis procera* roots, leaves, and blooms is utilized to localize the anticancer effect. On the T47D breast cancer cell line, this test was carried out using the MTT method. On the T47D breast cancer cell line, the base of *Calotropis procera* was more cytotoxic (IC₅₀ 89.76 g/ml) than the leaves and blooms. In light of the outcome, attaches are intense to be chemotherapeutic operators, especially in breast cancer [78].

The blossoms of *Calotropis procera* are widely used as a natural prescription characteristic of the old days. In this context, we will assess the targets of the antibacterial and anticancer properties of *Calotropis procera* extricate. The procedures used to screen the phytochemicals are UV-Vis and FTIR. Using the sequential stock weakening method, the antibacterial property of the concentrate was assessed. By using MTT measurement on the HeLa cell line cell feasibility is achieved. The presence of phenolic mixtures is affirmed by UV-Vis top at 271nm. IR range affirms the presence of liquor or phenols, essential amines, aldehydes, alkanes, sulfoxide, and halogen mixes. Against *Enterococcus faecalis* (75µg/ml) and *K. pneumonia* (2µg/ml), the concentrate has demonstrated antibacterial action. The fluid ethanolic extricate concentrate of *Calotropis procera* indicated less movement on HeLa disease cell practicality even at higher fixation (1000µg/ml). Using spectroscopic procedures, possibilities of being an extraordinary incentive in the screening of phytoconstituents from the concentrate due to their effortlessness and cost viability. For the restraint of bacterial development, the concentrate is skilled and may conceivably be useful for strengthening likely antimicrobial mixes. The investigation provides the most punctual logical proof to additional exploration in cleansing the mixes from the watery ethanolic extract and screening their adequacy [79].

Plants contain numerous organically dynamic particles with various therapeutic properties. India is incredibly rich in characteristic assets and therefore information on conventional medication and, in this way, the use of plants as a wellspring of ongoing medications is an intrinsic and truly significant part of the medical services framework. Regardless, almost no data is available about many valuable species as exploratory information. *Calotropis procera* Family Asclepiadaceae could be a xerophytic, erect bush, developing generally all through the tropical and subtropical districts of Asia and Africa. This plant is prominently known in light of the fact that it produces an extraordinary amount of latex. Latexes are a wellspring of arranged naturally dynamic mixes, including glycosides, tannins, and bunches of proteins, among others. The use of various pieces of the plant has prompted its utilization for spreading disease [80] and also to machine as a counteractant for snake harming [81].

The plant has expected pharmacological properties. The splitting of the latex into its free elastic and elastic divisions makes it possible to better knowledge of its possibilities and obstacles. This examination is planned to pass judgment on the antimicrobial and anticancer exercises of *Calotropis procera* latex separately against unmistakable human pathogens. The extracted latex has subjectively decomposed for the presence of different phytochemicals. Recently, the antimicrobial and anticancer action of the latex of *Calotropis procera* has been evaluated [82].

2.9. The Treatment of Different Irresistible Sickness

Since ancient times, plants have been misused as a restorative source. In the treatment of different irresistible sicknesses, the conventional and people therapeutic framework utilizes plant items. In recent times, plants have generally been widely studied for their restorative covering properties. Plants are the major source of drug discovery and advancement. It is explained that plants have antimicrobial, anticancer, mitigating, cell reinforcement, antidiabetic, hemolytic, and larvicidal properties. *Calotropis procera* is a no man's land weed and is also known as milkweed. The Natural surroundings of Asian nations include China, Malaysia, Indonesia, India, the Philippines, Sri Lanka, Thailand, and Pakistan. In the ancestral region, individuals use these plant parts to cure a few sicknesses, for example, toothache, ear infection, sprain, uneasiness, torment, epilepsy, loose bowels, and mental problems [83].

Calotropis procera is deductively revealed for its anticancer and antimicrobial movement. The current examination is a research center on the antimicrobial and anticancer movement of rough concentrate of *Calotropis procera* against clinical separates of microorganisms [84].

People and their predecessors have consistently been burdened with disease. There are sure diseases that have no solution, except for executives, which are made by suggestive concealment. Such viral, antitoxin-safe bacterial, contagious, and malignant infections make an icy mass of network issues. A colossal portion of the monetary supply is devoted to the administration of such untreatable illnesses, which is not good for the financial development of the country and the network of government assistance. Plants are used as a medication by an individual in any event to the center Paleolithic age approximately 60,000 years back.

The assortment of plants began to improve the conventional clinical framework and the assortment of plants as a method for treatment can be followed back just to the extent recorded reports of their resemblance. Almost 65% of the world's population has consolidated into their prime methodology of medical care as indicated by the World Wellbeing Association (WWA) [85]. Pakistan is advanced in indigenous restorative greenery which is not deductively explored at this point. Ethnobotanical confirmations are available which demonstrate some significant restorative employments of nearby vegetation. *Calotropis* is one of these unexplored therapeutic plants from nearby verdure which is usually used by medical professionals. Anticancer, antibacterial, antiviral, and antifungal impact of *Calotropis procera* is expected [84].

2.10. Assessment of Pharmacological Exercises of *Calotropis procera*

In this exploration, it is planned to assess the pharmacological exercises of *Calotropis procera* to solve the network problems from nearby vegetation. The motivation behind plants utilizing as an establishment of the remedial operators are:

- The partition of bioactive specialists for straight use as a medication.
- The creation of bioactive operators of new or not referred to structures as a primary blend for the semi-combination to deliver patentable substances of more prominent movement or/and least poisonousness.

In cutting-edge medication, the use of plant sources against oxidants, hostile to bacteria, hostile to contagious and malignancy is still in the starting stage. *Calotropis procera* is a plant that has a known enemy of oxidants, hostile to bacterial, against viral, and hostile to malignant growth action [86].

In-stream circumstances of clinical and medication progress, life forms remember the distinction of their processing and their inherited structure to be immune to prescriptions used in the treatment of standard powerful ailments. These prescription-safe candidates are more pathogenic with high mortality rates and are becoming an unimaginable test in the medication and clinical administration industry. To beat microbial drug safety,

specialists eagerly await the progression of choice and novel prescriptions. Trademark sources, for instance, plants, green development, and animals offer an assortment of typical helpful blends for the treatment of various overwhelming contaminations [20].

Plants have been misused as a therapeutic source since old age. The conventional and people restorative framework uses plant items for the treatment of different irresistible ailments. Lately, plants have been widely studied to have therapeutic properties. Studies by different specialists have demonstrated that plants are one of the significant hotspots for drug disclosure and advancement [41].

Plants are accounted for to have antimicrobial, anticancer, mitigating, antidiabetic, hemolytic, cancer prevention agent, and larvicidal properties. Although advances in conventional treatment approaches chemotherapy, radiotherapy, biological therapy, hormone therapy, and surgery, breast cancer (MCF-7) remains a major health problem due to the problem of drug resistance, some side effects, and aggressive behavior of tumors. Plants provided a source of motivation for novel medication complexes and their role in the progress of new drugs is two-fold: phyto medication to be used for the treatment of different diseases and a natural source for the formation of new drugs.

Medicinal plant extract contains novel therapeutic agents against human breast cancer cells [79]. Natural products contain a variety of medically important agents such as antibacterial, anticancer, immunosuppressant, and anticoagulant agents. These medicinal plants have novel therapeutic agents that are used to treat approximately 87% of all classified disorders. New treatment targets, different medications, and clinical approaches are therefore urgently required in order to fight more effectively against this complex form of tumor [87]. Natural products are acquired widely from plants and are an important part of contemporary medicinal products. Natural products derived from plants have been indicated to be the main sources of novel drugs such as morphine, topotecan, paclitaxel, quinine, and artemisinin. A lot of research has been done since antiquity in order to discover natural products with possible anticancer properties, such as etoposides, topotecan, vinblastine, paclitaxel, vinblastine, vincristine and docetaxel irinotecan etc. have been successfully used in cancer therapy. Around 1940 to 2002, 69% among approved drugs were either natural or data-based compounds.

2.11. The Use of Natural Products in Cancer Treatment

The use of natural products in cancer treatment appears to be progressive, providing the basis for modern medicine and providing a vast source of potential medicines. The primary sources, such as fruits and vegetables, for vitamins, minerals, dietary fiber, and other bioactive compounds. Plants were generally used for many thousands of years for the treatment of various diseases [65]. NPs in cancer recovery have been made until now. The new NPs have been bolstered by new technologies, such as high-performance tests on natural foods in plants, livestock, micro-organisms, and oceanic organisms. Therapeutic agents or products derived from plants are also considered to be healthier constituents than the discovery and development of synthetic drugs [88]. Plant compounds that have been extracted are of great value for protection, cost efficiency, improved bioavailability, and minimum side effects [20].

The first records of medicinal use date from about 2000 BC and indicates the presence in Mesopotamia of a complex medical system comprising about 1000 drugs derived from plants in general. The Egyptian medicinal system dates back to around 2800 BC, but its most useful records are "Ebers Papyrus" from 1550 BC with over 700 drugs mainly extracted from plant medicinal items. Plant kingdoms of about 250 thousand plant species have been investigated and only 10% for treating different disease conditions have been studied [62].

Phytochemicals are bioactive compounds derived from herbal start and harvest plants. Such compounds are effective in conjunction with cancer as they have anti-carcinogenic characteristics. Inconvenient truths have shown that the anti-carcinogenic

effects of phytochemicals are due to their antioxidant, anti-proliferative activities, anti-inflammatory, and anti-angiogenic [89]. Natural products have an interesting character in the prevention and treatment of several disorders. The valuable natural products have proven to be effective drugs to improve human health. In the past, Traditional Chinese medicine (TCM) has often been recognized by the medical community as a success [84]. Natural medicinal products have proved to be a key source of pharmaceutical narrative agents. Herbal medicine has held and continues to occupy an essential role in healthcare services in Chinese and Western countries, as a productive source of novel molecules [74].

Generally, medicinal plants have been used and illustrate certain pharmacological properties in traditional medicine. They treat cancer as well as playing an important role in the treatment of various cardiovascular disorders. The pharmaceutical industry uses therapeutic plants in the manufacture of drugs although bioactive chemical components are quite useful for making such medicines. Due to protection, oral management, and a limited budget, phytochemicals are able to prevent cancer [90].

In recent times, a huge number of plants as an interdisciplinary method of medicine for microbes' defense and control have been examined for their antifungal properties. Antimicrobial capacity for treating human microbial diseases can be quite important for the use of plant extracts. In the plant protection system, biologically active natural plant substances play a crucial role and are known for their explicit physiology on the human body. The main plant compounds are amino acids, popular proteins, sugar, and chlorophyll. Thus alkaloids, saponins, tannins, flavonoids, and terpenoids constitute secondary metabolites. Although secondary metabolites have enormous importance as therapeutic agents and as alternative or supportive drugs, they have become part of the interdisciplinary healthcare system. Flavonoid is a large phytochemicals family that includes flavanol, flavone, flavonol, flavanone, anthocyanins, proanthocyanidins, and isoflavone [68].

Medicinal plants are quite effective in the treatment of different types of cancer as they minimize toxicity. Different plants have demonstrated highly effective anticancer behaviors *in vitro* and *in vivo*. The main compounds for cancer treatment are polyphenols, terpenoids, and alkaloids. Rohitukine, paclitaxel, harringtonine, paclitaxel, and camptothecin are anti-cancer alkaloid compounds isolated from plants [79]. Plants are used as a source of drugs for the treatment of diseases and other illnesses in many countries, and plants have produced some of the most effective and potent drugs currently used. A variety of herbal medicines have been used in different plants (roots, fruit, stem, bloom, altered plant parts, and exudated twigs) with different medicinal activities. These are collected on a small scale to be used by local and traditional healers, while many more are collected as raw resources in larger quantities to be sold for various herbal industries. Plants are used in several countries to cure diseases and other illnesses as a source of medicines, some of the best and most effective medications used today are herbal medicine.

Calotropis procera has reported molluscicidal, antioxidant, and thrombolytic properties used for cancer treatment. *Calotropis procera* scavenges free radicals and dampens oxidative cell damage related to stress during ischemia; this means that it also has an antioxidant impact [84]. The maximum antioxidant activity of *Calotropis procera* has been recorded in the methylated spirit fraction ($IC_{50}=10.69\pm 1.66$) followed by the methanol fraction ($IC_{50}=9.10\pm 0.76$) and no activity was recorded in the hexane fraction. Good results indicate the antifungal and antimicrobial activity of *Calotropis procera* against *S. aureus*, *P. aeruginosa*, *S. aureus*, and *Aspergillus flavus*. The antimicrobial activity of its flavonoids was recently reported, while nutritional values of this and other wild-growing species in the Indian Rajasthan region have also been assessed [91].

2.12. The Commercial Use of Drugs

The commercial use of drugs has led to the development of drug resistance for the treatment of infectious diseases in human pathogenic microorganisms. Additionally, various side effects such as hypersensitivity, immune suppression, and allergic reactions are rarely associated with antibiotics. In various traditional systems, prehistoric use of natural products, including herbal fractions and isolation of anti-microbes, has proven to be safe and effective. The latest development in herbal anti-microbial use has increased and shown its importance. The boiled residue of *Calotropis procera* plant, especially paste is applied externally to tumors and other neck swellings. In the ethnic medicine system, plant aqueous extract is a popular remedy for cancer [78].

A broad-spectrum antimicrobial against gram-positive, gram-negative, spore-forming, and acid-fast bacteria were found in the raw extract of *Calotropis procera* from Sinai. In earlier studies on the medicinal value of *Calotropis procera* species, several biologically active chemical components are known [92]. Saponins, coumarins, alkaloids, and chlorides contain almost as much Callus as the intact leaf. Such findings coincide with others who found that *Calotropis procera* species contain protein, coumarins, amino acids, trace elements saponins, alkaloids, terpenoids, sterols, and flavonoids. The effectiveness of flavonoids and tannins is possible as they have the ability to associate with the protein which is extracellular and soluble leading to killing the bacteria by interfering with the cell walls of bacteria. NF- κ B controls the expression of the inflammatory mediators. Some herbal compounds Flavonoids classified as NF- κ B inhibitors are stated to be inhibited [93].

Calotropis procera local name is Aak. Pakistan is historically well known for the use of conventional internal and external formulations for treating acne, leprosy, sores, hemorrhoids, open injuries, and fiber. Anti-inflammatory, analgesic, antipyretic, or thrombolytic effects were also identified as a consequence of *Calotropis procera* species. A variety of chemical components have already been identified in various *Calotropis procera* spp, such as terpenoids, saponins, flavonoid Glycosides, etc. [94]. Except for Australia, the group has 35 species that are limited to India's warm and arid areas, as well as all continents, including eastward Pakistan (NWFP, Punjab, Balochistan, and Sindh). *Calotropis procera* possesses bioactive and therapeutic characteristics.

Calotropis procera has anticoagulant properties and further demonstrated that *Calotropis procera* has the active anticoagulant property and includes many phytochemicals after part-characterization. The most effective approach was the plasma recalcification procedure for examining new drugs [95].

3. Conclusions

Many academics have recently looked at the pharmacological significance of therapeutic plants. This is partly owing to the fact that these plants have been utilized in traditional medicine for ages as treatments for a variety of ailments. Furthermore, these plants' extracts have few side effects, making them attractive candidates for medication development. Our preliminary findings support the importance of *C. procera* methanolic leaf extract as an anticancer and antibacterial agent. It effectively stopped MRSA from growing, which is a potential concern to people due to its antibiotic resistance. Its efficiency against the MCF7 cell line is also commendable. In addition, *in vivo* investigations are needed to provide light on the method of action of this medicinally significant plant, and the isolation of individual components might aid in the development of medicines with fewer adverse effects.

3.1. Clinical Implications

The implications of *Calotropis procera* for all healthcare professionals including oncologists, physicians, pharmacists, nurses, and nutritional therapists are significant. With the increasing incidence of cancer and antibiotic-resistant bacterial infections, there

is a growing need for new, effective treatments. *Calotropis procera* offers a potential solution to both these problems. Its anticancer properties make it a promising candidate for the development of new cancer treatments, while its antibacterial properties make it a potential alternative to antibiotics.

However, there are also some potential risks associated with the use of *Calotropis procera*. For example, the plant contains toxic compounds, such as calotropin and uscharin, which can be harmful if ingested in large quantities. As such, healthcare professionals, especially physicians, clinical pharmacists, and nurses must exercise caution when using the plant and ensure that appropriate dosages are administered to patients.

Author Contributions: MA is the corresponding author of the study and conceived the study. SR performed references collection, AR drafted the paper, and UL reviewed the manuscript. RZ performed editing of the manuscript. MK and HM reviewed the manuscript, MBS and HSA proofread the final version, while MAS and HHA submitted the manuscript for publishing. All authors provided input regarding the manuscript and approved the final version.

Funding: This review article received no external funding.

Data Availability Statement: All data are represented in the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

- [1] Arzu Ü. The Importance Of Microbial Genetic Resources For Food And Agriculture In The Bioeconomy. *Journal of Agriculture*. **2020**;3(1):33-42 DOI: 10.46876/ja.734775.
- [2] Sheppard SK, Guttman DS, Fitzgerald JR. Population genomics of bacterial host adaptation. *Nature reviews Genetics*. **2018**;19(9):549-65 DOI: 10.1038/s41576-018-0032-z.
- [3] Toghueo RMK. Bioprospecting endophytic fungi from *Fusarium* genus as sources of bioactive metabolites. *Mycology*. **2020**;11(1):1-21 DOI: 10.1080/21501203.2019.1645053.
- [4] van der Lee R, Buljan M, Lang B, Weatheritt RJ, Daughdrill GW, Dunker AK, et al. Classification of intrinsically disordered regions and proteins. *Chem Rev*. **2014**;114(13):6589-631 DOI: 10.1021/cr400525m.
- [5] Bremer E, Kramer R. Responses of Microorganisms to Osmotic Stress. *Annu Rev Microbiol*. **2019**;73:313-34 DOI: 10.1146/annurev-micro-020518-115504.
- [6] Rosenberg E, Koren O, Reshef L, Efrony R, Zilber-Rosenberg I. The role of microorganisms in coral health, disease and evolution. *Nature reviews Microbiology*. **2007**;5(5):355-62 DOI: 10.1038/nrmicro1635.
- [7] Pereira FC, Berry D. Microbial nutrient niches in the gut. *Environ Microbiol*. **2017**;19(4):1366-78 DOI: 10.1111/1462-2920.13659.
- [8] Hasan M, Sultan M, Mar-E-Um M. Significance of fermented food in nutrition and food science. *Journal of Scientific Research*. **2014**;6(2):373-86 DOI: 10.3329/jsr.v6i2.16530.
- [9] Falkow S. Molecular Koch's postulates applied to bacterial pathogenicity — a personal recollection 15 years later. *Nature Reviews Microbiology*. **2004**;2(1):67-72 DOI: 10.1038/nrmicro799.
- [10] Bang C, Schmitz RA. Archaea associated with human surfaces: not to be underestimated. *FEMS microbiology reviews*. **2015**;39(5):631-48 DOI: 10.1093/femsre/fuv010.
- [11] Bernstein H, Bernstein C, Michod RE. Sex in microbial pathogens. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*. **2018**;57:8-25 DOI: 10.1016/j.meegid.2017.10.024.
- [12] Farkas J. Irradiation as a method for decontaminating food: a review. *International journal of food microbiology*. **1998**;44(3):189-204 DOI: 10.1016/s0168-1605(98)00132-9.
- [13] Abdel-Aziz SM, Asker MM, Keera AA, Mahmoud MG. Microbial food spoilage: control strategies for shelf life extension. *Microbes in food and health: Springer*; 2016. p. 239-64 DOI: 10.1007/978-3-319-25277-3_13.
- [14] Force USPST, Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, et al. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. **2018**;320(7):674-86 DOI: 10.1001/jama.2018.10897.
- [15] Bahrami A, Khazaei M, Shahidsales S, Hassanian SM, Hasanzadeh M, Maftouh M, et al. The Therapeutic Potential of PI3K/Akt/mTOR Inhibitors in Breast Cancer: Rational and Progress. *J Cell Biochem*. **2018**;119(1):213-22 DOI: 10.1002/jcb.26136.

- [16] AML AML. Haematacon 2013 (54th Annual Conference of Indian Society of Haematology & Blood Transfusion). *Indian J Hematol Blood Transfus (Oct-Dec 2013)*. **2013**;29(4):278-400 DOI: 10.1007/s12288-013-0302-z.
- [17] Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annual review of genetics*. **2005**;39:359-407 DOI: 10.1146/annurev.genet.39.110304.095751.
- [18] Monei T, Pedro A. A systematic review of interventions for children presenting with dyscalculia in primary schools. *Educational Psychology in Practice*. **2017**;33(3):277-93 DOI: 10.1080/02667363.2017.1289076.
- [19] Motofei IG. Biology of Cancer; From Cellular Cancerogenesis to Supracellular Evolution of Malignant Phenotype. *Cancer Invest*. **2018**;36(5):309-17 DOI: 10.1080/07357907.2018.1477955.
- [20] Wahabi K, Perwez A, Rizvi MA. Parkin in Parkinson's disease and cancer: a double-edged sword. *Molecular Neurobiology*. **2018**;55(8):6788-800 DOI: 10.1007/s12035-018-0879-1.
- [21] Pernas L, Scorrano L. Mito-morphosis: mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. *Annual review of physiology*. **2016**;78:505-31 DOI: 10.1111/1462-2920.13659.
- [22] Xiao M, Whitnall MH. Pharmacological countermeasures for the acute radiation syndrome. *Curr Mol Pharmacol*. **2009**;2(1):122-33 DOI: 10.2174/1874467210902010122.
- [23] Wennberg JE, Fisher ES, Skinner JS. Geography And The Debate Over Medicare Reform: A reform proposal that addresses some underlying causes of Medicare funding woes: geographic variation and lack of incentive for efficient medical practices. *Health affairs*. **2002**;21(Suppl1):W96-W112 DOI: 10.1377/hlthaff.w2.96.
- [24] Leber MF, Efferth T. Molecular principles of cancer invasion and metastasis (review). *Int J Oncol*. **2009**;34(4):881-95 DOI: 10.3892/ijco_00000214.
- [25] Palmer TD, Ashby WJ, Lewis JD, Zijlstra A. Targeting tumor cell motility to prevent metastasis. *Adv Drug Deliv Rev*. **2011**;63(8):568-81 DOI: 10.1016/j.addr.2011.04.008.
- [26] Aoi W, Naito Y, Takagi T, Tanimura Y, Takanami Y, Kawai Y, et al. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. *Gut*. **2013**;62(6):882-9 DOI: 10.1136/gutjnl-2011-300776.
- [27] Slavney AH, Hu T, Lindenberg AM, Karunadasa HI. A Bismuth-Halide Double Perovskite with Long Carrier Recombination Lifetime for Photovoltaic Applications. *J Am Chem Soc*. **2016**;138(7):2138-41 DOI: 10.1021/jacs.5b13294.
- [28] Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA*. **2006**;296(2):193-201 DOI: 10.1001/jama.296.2.193.
- [29] Phan AT, Gueron M, Leroy JL. The solution structure and internal motions of a fragment of the cytidine-rich strand of the human telomere. *J Mol Biol*. **2000**;299(1):123-44 DOI: 10.1006/jmbi.2000.3613.
- [30] Sotiropoulos SK, Kamileri I, Lugli N, Evangelou K, Da-Re C, Huber F, et al. Mammalian RAD52 Functions in Break-Induced Replication Repair of Collapsed DNA Replication Forks. *Mol Cell*. **2016**;64(6):1127-34 DOI: 10.1016/j.molcel.2016.10.038.
- [31] Kreitler S. Determinants, Risk Factors, and Protective Factors for Cancer: Environmental, Physiological, and Demographic. *Psycho-Oncology for the Clinician*: Springer; 2019. p. 45-62 DOI: 10.26444/aaem/94299.
- [32] Mileo AM, Miccadei S. Polyphenols as modulator of oxidative stress in cancer disease: new therapeutic strategies. *Oxidative medicine and cellular longevity*. **2016**;2016 DOI: 10.1155/2016/6475624.
- [33] Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. **2018**;359(6378):926-30 DOI: 10.1126/science.aar3247.
- [34] Kuo CN, Liao YM, Kuo LN, Tsai HJ, Chang WC, Yen Y. Cancers in Taiwan: Practical insight from epidemiology, treatments, biomarkers, and cost. *Journal of the Formosan Medical Association = Taiwan yi zhi*. **2020**;119(12):1731-41 DOI: 10.1016/j.jfma.2019.08.023.
- [35] Damiati S, Peacock M, Mhanna R, Sørstad S, Sleytr UB, Schuster B. Bioinspired detection sensor based on functional nanostructures of S-proteins to target the folate receptors in breast cancer cells. *Sensors and Actuators B: Chemical*. **2018**;267:224-30 DOI: 10.1016/j.snb.2018.04.037.
- [36] Evans C, Hamilton RJ, Tercyak KP, Peshkin BN, Rabemananjara K, Isaacs C, et al., editors. Understanding the needs of young women regarding breast cancer risk assessment and genetic testing: convergence and divergence among patient-counselor perceptions and the promise of peer support. Healthcare; 2016: Multidisciplinary Digital Publishing Institute.
- [37] Muhammad DRA, Kongor JE, Dewettinck K. Investigating the effect of different types of cocoa powder and stabilizers on suspension stability of cinnamon-cocoa drink. *J Food Sci Technol*. **2021**;58(10):3933-41 DOI: 10.1007/s13197-020-04855-y.
- [38] DeSantis CE, Miller KD, Dale W, Mohile SG, Cohen HJ, Leach CR, et al. Cancer statistics for adults aged 85 years and older, 2019. *CA Cancer J Clin*. **2019**;69(6):452-67 DOI: 10.3322/caac.21577.
- [39] Hammad HM, Ashraf M, Abbas F, Bakhat HF, Qaisrani SA, Mubeen M, et al. Environmental factors affecting the frequency of road traffic accidents: a case study of sub-urban area of Pakistan. *Environmental science and pollution research international*. **2019**;26(12):11674-85 DOI: 10.1007/s11356-019-04752-8.
- [40] Falcetta FS, Träsel HdAV, de Almeida FK, Falcetta MRR, Falavigna M, Rosa DD. Effects of physical exercise after treatment of early breast cancer: systematic review and meta-analysis. *Breast cancer research and treatment*. **2018**;170(3):455-76 DOI: 10.1007/s10549-018-4786-y.
- [41] Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk Factors and Preventions of Breast Cancer. *Int J Biol Sci*. **2017**;13(11):1387-97 DOI: 10.7150/ijbs.21635.

- [42] Brown ZJ, Heinrich B, Greten TF. Mouse models of hepatocellular carcinoma: an overview and highlights for immunotherapy research. *Nature reviews Gastroenterology & hepatology*. **2018**;15(9):536-54 DOI: 10.1038/s41575-018-0033-6.
- [43] Jolivald CG, Frizzi KE, Guernsey L, Marquez A, Ochoa J, Rodriguez M, et al. Peripheral Neuropathy in Mouse Models of Diabetes. *Curr Protoc Mouse Biol*. **2016**;6(3):223-55 DOI: 10.1002/cpmo.11.
- [44] George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. **2015**;524(7563):47-53 DOI: 10.1038/nature14664.
- [45] Proia TA, Keller PJ, Gupta PB, Klebba I, Jones AD, Sedic M, et al. Genetic predisposition directs breast cancer phenotype by dictating progenitor cell fate. *Cell Stem Cell*. **2011**;8(2):149-63 DOI: 10.1016/j.stem.2010.12.007.
- [46] Keshet R, Szlosarek P, Carracedo A, Erez A. Rewiring urea cycle metabolism in cancer to support anabolism. *Nature reviews Cancer*. **2018**;18(10):634-45 DOI: 10.1038/s41568-018-0054-z.
- [47] Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis*. **2018**;5(2):77-106 DOI: 10.1016/j.gendis.2018.05.001.
- [48] Leong SP, Shen Z-Z, Liu T-J, Agarwal G, Tajima T, Paik N-S, et al. Is breast cancer the same disease in Asian and Western countries? *World journal of surgery*. **2010**;34(10):2308-24 DOI: 10.1007/s00268-010-0683-1.
- [49] Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. **2017**;27(3):315-89 DOI: 10.1089/thy.2016.0457.
- [50] Dawney L. Decommissioned places: Ruins, endurance and care at the end of the first nuclear age. *Transactions of the Institute of British Geographers*. **2020**;45(1):33-49 DOI: 10.1111/tran.12334.
- [51] Afsharfard A, Mozaffar M, Orang E, Tahmasbpour E. Trends in epidemiology, clinical and histopathological characteristics of breast cancer in Iran: results of a 17 year study. *Asian Pacific Journal of Cancer Prevention*. **2013**;14(11):6905-11 DOI: 10.7314/apjcp.2013.14.11.6905.
- [52] Salem ME, Puccini A, Grothey A, Raghavan D, Goldberg RM, Xiu J, et al. Landscape of Tumor Mutation Load, Mismatch Repair Deficiency, and PD-L1 Expression in a Large Patient Cohort of Gastrointestinal Cancers. *Molecular cancer research : MCR*. **2018**;16(5):805-12 DOI: 10.1158/1541-7786.MCR-17-0735.
- [53] Bergamaschi A, Kim YH, Wang P, Sørlie T, Hernandez-Boussard T, Lonning PE, et al. Distinct patterns of DNA copy number alteration are associated with different clinicopathological features and gene-expression subtypes of breast cancer. *Genes, Chromosomes and Cancer*. **2006**;45(11):1033-40 DOI: 10.1002/gcc.20366.
- [54] Sinkovics JG. Horizontal gene transfers with or without cell fusions in all categories of the living matter. *Cell Fusion in Health and Disease*. **2011**:5-89 DOI: 10.1007/978-94-007-0782-5_2.
- [55] González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *New England Journal of Medicine*. **2019**;381(25):2391-402 DOI: 10.1056/NEJMoa1910962.
- [56] Hoarau-Véchet J, Rafii A, Touboul C, Pasquier J. Halfway between 2D and animal models: are 3D cultures the ideal tool to study cancer-microenvironment interactions? *International journal of molecular sciences*. **2018**;19(1):181 DOI: 10.3390/ijms19010181.
- [57] Jaeschke H, McGill MR, Ramachandran A. Oxidant stress, mitochondria, and cell death mechanisms in drug-induced liver injury: lessons learned from acetaminophen hepatotoxicity. *Drug Metab Rev*. **2012**;44(1):88-106 DOI: 10.3109/03602532.2011.602688.
- [58] Ispanovic E, Haas TL. JNK and PI3K differentially regulate MMP-2 and MT1-MMP mRNA and protein in response to actin cytoskeleton reorganization in endothelial cells. *American journal of physiology Cell physiology*. **2006**;291(4):C579-88 DOI: 10.1152/ajpcell.00300.2005.
- [59] Li J, Li A, Li M, Liu Y, Zhao W, Gao D. Ginkgolic acid exerts an anti-inflammatory effect in human umbilical vein endothelial cells induced by ox-LDL. *Die Pharmazie*. **2018**;73(7):408-12 DOI: 10.1681/ph.2018.8397.
- [60] Martín-Rodríguez AJ, Quezada H, Becerril G, Maeda VP, Wood TK, García-Contreras R. Recent advances in novel antibacterial development. *Frontiers in Clinical Drug Research: Anti-Infectives*. **2016**;2:3-61 DOI: 10.2174/9781681081533116020003.
- [61] Allawadhi P, Khurana A, Sayed N, Kumari P, Godugu C. Isoproterenol-induced cardiac ischemia and fibrosis: Plant-based approaches for intervention. *Phytotherapy Research*. **2018**;32(10):1908-32 DOI: 10.1002/ptr.6152.
- [62] Hart NH, Galvao DA, Newton RU. Exercise medicine for advanced prostate cancer. *Curr Opin Support Palliat Care*. **2017**;11(3):247-57 DOI: 10.1097/SPC.0000000000000276.
- [63] Atkinson CW. *The Oldest Vocation: Christian Motherhood in the Medieval West* Cornell University Press; 2019. DOI.
- [64] Al-Hatamleh MAI, Hatmal MM, Sattar K, Ahmad S, Mustafa MZ, Bittencourt MC, et al. Antiviral and Immunomodulatory Effects of Phytochemicals from Honey against COVID-19: Potential Mechanisms of Action and Future Directions. *Molecules*. **2020**;25(21):5017 DOI: 10.3390/molecules25215017.
- [65] Flinn AM, Gennery AR. Treatment of Pediatric Acute Graft-versus-Host Disease—Lessons from Primary Immunodeficiency? *Frontiers in immunology*. **2017**;8:328 DOI: 10.3389/fimmu.2017.00328.
- [66] Abd El-Rahman TM, El-Beih AA, Ali AM, Salah MG. Antimicrobial Potential of *Paenibacillus Polymyxa* AALI Endophyte Isolated from *Calotropis Procera*. *International Journal of Progressive Sciences and Technologies*. **2020**;20(2):418-22 DOI.

- [67] Ali A, Ansari A, Ul Qader SA, Mumtaz M, Saied S, Mahboob T. Antibacterial potential of *Calotropis procera* (flower) extract against various pathogens. *Pakistan journal of pharmaceutical sciences*. **2014**;27 DOI.
- [68] Abegunde Segun M, Akinyele Simeon A, Ayodele-Oduola Roseline O. Chemical analysis and antibacterial activities of *Calotropis procera* and *Clusia rosea* leaves extracts. *GSC Biological and Pharmaceutical Sciences*. **2020**;12(1):025-30 DOI: 10.30574/gscbps.2020.12.1.0175.
- [69] Ali M, Haroon U, Khizar M, Chaudhary HJ, Munis MFH. Facile single step preparations of phyto-nanoparticles of iron in *Calotropis procera* leaf extract to evaluate their antifungal potential against *Alternaria alternata*. *Current Plant Biology*. **2020**;23:100157 DOI: 10.1016/j.cpb.2020.100157.
- [70] Muthuvel A, Jothibas M, Mohana V, Manoharan C. Green synthesis of cerium oxide nanoparticles using *Calotropis procera* flower extract and their photocatalytic degradation and antibacterial activity. *Inorganic Chemistry Communications*. **2020**;119:108086 DOI: 10.1016/j.inoche.2020.108086.
- [71] Malathi S, Lahari S, Rajani K, Sampagavi MSM, Sushma MSM. A Total Survey On Leaves Of *Melaleuca Alternifolia* (Tea Tree Oil). *World Journal of Current Medical and Pharmaceutical Research*. **2020**:271-9 DOI: 10.37022/wjcmpr.vi.152.
- [72] Al-Snafi AE. Pharmacological importance of *Haplophyllum* species grown in Iraq-A review. *IOSR Journal of Pharmacy*. **2018**;8(5):54-62 DOI.
- [73] Naser EH, Kashmer AM, Abed SA. Antibacterial activity and phytochemical investigation of leaves of *Calotropis procera* plant in Iraq by GC-MS. *IJPSR*. **2019**;10(4):1988-94 DOI: 10.13040/IJPSR.0975-8232.10(4).1988-94.
- [74] Pattnaik PK, Kar D, Chhatoi H, Shahbazi S, Ghosh G, Kuanar A. Chemometric profile & antimicrobial activities of leaf extract of *Calotropis procera* and *Calotropis gigantea*. *Nat Prod Res*. **2017**;31(16):1954-7 DOI: 10.1080/14786419.2016.1266349.
- [75] Gashgari R, Gherbawy Y, Ameen F, Alsharari S. Molecular Characterization and Analysis of Antimicrobial Activity of Endophytic Fungi From Medicinal Plants in Saudi Arabia. *Jundishapur J Microbiol*. **2016**;9(1):e26157 DOI: 10.5812/jjm.26157.
- [76] Khan AAH. Cytotoxic potential of plant nanoparticles. *Nanobiotechnology applications in plant protection*: Springer; 2019. p. 241-65 DOI: 10.1007/978-3-030-13296-5_13.
- [77] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. **2015**;136(5):E359-86 DOI: 10.1002/ijc.29210.
- [78] Mutiah R, Sukardiman S, Widyawaruyanti A, Zulaikeh S. Comparison of Ethanol Extract from Roots, Leaves, and Flowers of *Calotropis gigantea* as Anticancer on T47D Breast Cancer Cell Lines. *Alchemy*. **2016**;5(1):1-4 DOI: 10.18860/al.v5i1.3690.
- [79] Gururaja K, David M. Spectroscopic signature, antibacterial and anticancer properties of *Calotropis gigantea* (Linn.) flower. *International Journal of Pharmaceutical Sciences and Research*. **2016**;7(4):1686 DOI: 10.13040/IJPSR.0975-8232.7(4).1686-93.
- [80] Basu A, Chaudhuri AK. Preliminary studies on the antiinflammatory and analgesic activities of *Calotropis procera* root extract. *J Ethnopharmacol*. **1991**;31(3):319-24 DOI: 10.1016/0378-8741(91)90017-8.
- [81] Greenwell M, Rahman P. Medicinal plants: their use in anticancer treatment. *International journal of pharmaceutical sciences and research*. **2015**;6(10):4103 DOI: 10.13040/IJPSR.0975-8232.6(10).4103-12.
- [82] Biswasroy P, Panda S, Das D, Kar DM, Ghosh G. Pharmacological investigation of *Calotropis gigantea*: A benevolent herb of Nature. *Research Journal of Pharmacy and Technology*. **2020**;13(1):461-7 DOI: 10.5958/0974-360X.2020.00090.6.
- [83] Kuuluvainen T. Conceptual models of forest dynamics in environmental education and management: keep it as simple as possible, but no simpler. *Forest Ecosystems*. **2016**;3(1):1-9 DOI: 10.1186/s40663-016-0075-6
- [84] Rajkuberan C, Sudha K, Sathishkumar G, Sivaramakrishnan S. Antibacterial and cytotoxic potential of silver nanoparticles synthesized using latex of *Calotropis gigantea* L. *Spectrochimica acta Part A, Molecular and biomolecular spectroscopy*. **2015**;136 Pt B:924-30 DOI: 10.1016/j.saa.2014.09.115.
- [85] Sadgrove N, Jones G. A contemporary introduction to essential oils: chemistry, bioactivity and prospects for Australian agriculture. *Agriculture*. **2015**;5(1):48-102 DOI: 10.3390/agriculture5010048.
- [86] Vannette RL. The floral microbiome: plant, pollinator, and microbial perspectives. *Annual Review of Ecology, Evolution, and Systematics*. **2020**;51:363-86 DOI: 10.1146/annurev-ecolsys-011720-013401.
- [87] Corrêa RC, Heleno SA, Alves MJ, Ferreira IC. Bacterial Resistance: antibiotics of last generation used in clinical practice and the arise of natural products as new therapeutic alternatives. *Current pharmaceutical design*. **2020**;26(8):815-37 DOI: 10.2174/1381612826666200224105153.
- [88] Sampaio L, de Carvalho Mesquita Ayres JR. Critique of the concept of motivation and its implications for healthcare practices. *Philosophy, ethics, and humanities in medicine : PEHM*. **2019**;14(1):14 DOI: 10.1186/s13010-019-0083-6.
- [89] Younes SNMZ. Anticancer Activity of Guggulsterone in Human Leukemic Cells. *QSpace Institutional Repository*. **2020**;23(23):59-64 DOI: hdl.handle.net/10576/15222.
- [90] Kotecha R, Takami A, Espinoza JL. Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. *Oncotarget*. **2016**;7(32):52517-29 DOI: 10.18632/oncotarget.9593.
- [91] Mohamed NH, Ismail MA, Abdel-Mageed WM, Mohamed Shoreit AA. Antimicrobial activity of green silver nanoparticles from endophytic fungi isolated from *Calotropis procera* (Ait) latex. *Microbiology (Reading)*. **2019**;165(9):967-75 DOI: 10.1099/mic.0.000832.
- [92] Egbuna C, Mishra AP, Goyal MR. Preparation of phytopharmaceuticals for the management of disorders: the development of nutraceuticals and traditional medicine: Academic Press; 2020. DOI.

-
- [93] Chen C-YA, Chang JT, Ho Y-F, Shyu A-B. MiR-26 down-regulates TNF- α /NF- κ B signalling and IL-6 expression by silencing HMGA1 and MALT1. *Nucleic acids research*. **2016**;44(8):3772-87 DOI: 10.1093/nar/gkw205.
- [94] Nenaah G. Antimicrobial activity of *Calotropis procera* Ait.(Asclepiadaceae) and isolation of four flavonoid glycosides as the active constituents. *World Journal of Microbiology and Biotechnology*. **2013**;29(7):1255-62 DOI: 10.1007/s11274-013-1288-2.
- [95] Bezerra CF, Mota EF, Silva ACM, Tome AR, Silva MZR, de Brito D, et al. Latex proteins from *Calotropis procera*: Toxicity and immunological tolerance revisited. *Chem Biol Interact*. **2017**;274:138-49 DOI: 10.1016/j.cbi.2017.07.007.