IJAREEIE

e-ISSN: 2278-8875
p-ISSN: 2320-3765

International Journal of Advanced Research

in Electrical, Electronics and Instrumentation Engineering

Volume 10, Issue 4, April 2021

INTERNATIONAL STANDARD SERIAL NUMBER INDIA

Impact Factor: 7.122

International Journal of Advanced Research in Electrical, Electronics and Instrumentation Engineering (IJAREEIE)

| e-ISSN: 2278 – 8875, p-ISSN: 2320 – 3765| www.ijareeie.com | Impact Factor: 7.122 | A Monthly Peer Reviewed & Referred Journal |

|| Volume 10, Issue 4, April 2021 ||

| DOI:10.15662/IJAREEIE.2021.1004051 |

Calotropis Procera and its Medicinal Uses

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ABSTRACT: *Calotropis procera* is a species of flowering plant in the family Apocynaceae that is native to Northern and Tropical Africa, Western Asia, South Asia and Indochina (mainland Southeast Asia). It typically reaches a height between 6 feet (1.8 m) to 8 feet (2.4 m), and rarely to as high as 15 feet (4.6 m), and grows in sunny to partly-shaded habitats such as disturbed and overgrazed lands, rangeland, roadsides, river flats and coastal dunes.[3] Its green fruits contain a toxic milky sap that is extremely bitter and turns into a latex-like substance, which is resistant to soap.

KEYWORDS-*Calotropis procera*, medicinal, latex, apocynaceae, desert, uses

I.INTRODUCTION

Common names for the plant include Apple of Sodom,[2] Sodom apple, roostertree,[3] king's crown,[4] small crownflower,[3] giant milkweed,[5] rubber bush,[2] and rubber tree.[2] The names "Apple of Sodom" and "Dead Sea Apple" stem from the ancient authors Josephus and Tacitus, who described the plant growing in the area of biblical Sodom.[6] Although not native to the New World, the plant (and other related milkweed species) has been cultivated, and feeds monarch butterfly caterpillars, in places such as California, Hawaii and the island of Puerto Rico.[3][5] In Arabic, it is known as *al-ashkhar*.[7]

History and traditional uses

Land of Israel

Some biblical commentators believe that the Sodom apple may have been the poisonous gourd (or poison-tasting gourd) that led to "death in the pot" in the Second Book of Kings (2 Kings 4:38–41). In this story, a well-meaning servant of the prophet Elisha gathers herbs and a large quantity of the unknown gourds, and casts them into the pot. After the outcry from the band of prophets, Elisha instructs them to cast flour into the stew pot, and they are saved.[8]

In 1938, botanists Hannah and Ephraim HaReuveni, authors of "The Squill and the Asphodel" (and parents of Noga HaReuveni), speculated that Jeremiah's *ar'ar/arow'er* was the Sodom apple.[9][10]

The fibre of the Sodom apple may have been used for the linen of the high priests.[*citation needed*]

Flower and fruit

The fruit is described by the Roman Jewish historian Josephus, who saw it growing near what he calls Sodom, near the Dead Sea: "...as well as the ashes growing in their fruits; which fruits have a color as if they were fit to be eaten, but if you pluck them with your hands, they dissolve into smoke and ashes."[11]

Sodom apple is listed in the Mishnah and Talmud. The fibers attached to the seeds may have been used as wicks. However the Mishnah forbids this for the Sabbath:[9] "It may not be lighted with cedar-bast, nor with uncombed flax, nor with floss-silk, nor with willow fiber, nor with nettle fiber. – Sabbath Chapter [1,2,3]

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In his *Biblical Researches in Palestine*, American biblical scholar Edward Robinson describes it as the fruit of the *Asclepias gigantea* vel *procera*, a tree 10–15 feet high, with a grayish cork-like bark called '*osher* by the Arabs. He says the fruit resembled "a large, smooth apple or orange, hanging in clusters of three or four." When "pressed or struck, it explodes with a puff, like a bladder or puff-ball, leaving in the hand only the shreds of the thin rind and a few fibers. It is indeed filled chiefly with air, which gives it the round form; while in the center a small slender pod runs through it which contains a small quantity of fine silk, which the Arabs collect and twist into matches for their guns."[6]

Bedouins of the Sinai and Negev traditionally made use of the fibers of this plant for making skull-caps (*tagiyah*).[13]

Middle East

Known as Sodom's Apple (Al Ashkhar) in the United Arab Emirates, it is a common desert shrub with a wide range of medicinal applications in traditional Bedouin medicine.[14] It has been linked to a number of cases of poisoning and corneal damage caused by children unknowingly touching its sap and then their eyes. Bedouin have long held that the plant causes blindness if contact is made with the eyes and any part of the plant. Its roots were traditionally burned and used as a component of gunpowder by Bedouin in the Trucial States.[15]

West Indies

The plant is known to occur throughout the tropical belt and is also common in the West Indies (e.g. Jamaica, Puerto Rico),[5] where the locals know it as "pillow cotton".[16] When the ripe "apples" burst, the fibrous contents are ejected along with the seeds.

South Africa

The giant milkweed is used for fibre and medicine in Southern Africa, but it rapidly invades subsistence agricultural fields reducing yields. The plant is poisonous if eaten by livestock. It thrives in the hot northern regions of Limpopo Province. This plant is also found along road verges and in drainage lines.[17]

Australia

In Australia, it is a weed of Western Australia, the Northern Territory, South Australia and Queensland.[18] It is thought to have arrived in the Northern Territory via the seeds which have tufts of silky hairs: the silky material (originating in Africa or Asia) having been used as padding in camel saddles.[19]

In the Northern Territory, it is found on alluvial plains, ephemeral watercourses and run-on areas. It also occurs on red earth plains and heavy soil plains.[20]

Toxicity

The milky sap contains a complex mix of chemicals, some of which are steroidal heart poisons known as "cardiac aglycones". These belong to the same chemical family as similar ones found in foxgloves (*Digitalis purpurea*).[

The plant contains steroidal components that are the cause of its toxicity. In the case of the Calotropis glycosides, their names are calotropin, calotoxin, calactin, uscharidin and voruscharin.[

Literary and musical references

John Milton alludes to this plant in his epic poem *Paradise Lost*[21] while describing the fruit that Satan and his cohorts eat after having tempted Adam and Eve to eat an apple from the tree of the knowledge of good and evil:

...greedy they pluck'd
The Frutage fair to sight, like that which grew
Neer that bituminous Lake where *Sodom* flam'd;
This more delusive, not the touch, but taste
Deceav'd; they fondly thinking to allay
Thir appetite with gust, instead of Fruit
Chewd bitter Ashes, which th' offended taste
With spattering noise rejected: oft they assayd
Hunger and thirst constraining...
—*Paradise Lost (2nd ed.) Book 10 lines 560–568*

Marilyn Manson recorded a song named "Apple of Sodom" for the soundtrack album of the 1997 David Lynch film *Lost Highway*.[4,5,6]

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II.DISCUSSION

Plants, which have been the unique source of remedies for thousands of years, have been used in management of human's as well as animals' diseases (El-seedi et al., 2019). Currently, medicinal plants (MPs) are still the major source of primary health care in developing countries (Mulat et al., 2020). As per the World Health Organisation (WHO), around 80% of world populace especially in developing countries rely on traditional medicines, particularly on MPs for their routine health problems (Fatima et al., 2018, Jamshidi-Kia et al., 2018, Amini et al., 2019). However, only around 50% of western drugs contain plants bioactive compounds or their analogues as their active ingredients (Gupta & Pandey, 2020).

Microbial infections have been the main cause of mortality, and resistant microorganisms are increasingly threatening the public health worldwide (Vidyasagar, 2016, Khameneh et al., 2019, Biharee et al., 2020). Currently, the annual number of deaths reaches 700,000 due to resistant pathogens out of which around 230,000 deaths occur only due to Multidrug-resistant (MDR) tuberculosis. The drug-resistant diseases are expected to cause 10 million deaths per year by 2050 (Biharee et al., 2020). Similarly, the incidence of fungal infections has increased dramatically since the past few decades that can be attributed to the abundant spread of fungal spores in the soil and in the air. Exposure to heavy fungal spores can cause several infections (e.g., sinusitis, lung, and skin infections) particularly in immunocompromised individuals (Vidyasagar, 2016).

Development of new drugs and newer strategies are strongly needed to combat resistance to antibiotics (Khameneh et al., 2019, Mulat et al., 2020). The WHO emphasises on discovery of new antimicrobial drugs against the resistant pathogens (WHO, 2019). Phytochemicals have shown different degrees of activity against microbial pathogens, and they are believed to produce no or lesser side effects when compared to synthetic antimicrobials (Konaté et al., 2012, Vidyasagar, 2016, Pathania et al., 2020). Some phytochemicals can reverse or modify the antimicrobial resistance (Chusri et al., 2009), or may produce synergistic effects with conventional antibiotics (Lee et al., 2010). Indeed, phytochemicals may act as antimicrobial agents through different mechanisms (Biharee et al., 2020). That is to say, co-administration of antibiotics with the non-antibiotic compounds that act as resistance breakers, could be one of the useful strategy to enhance or restore antibiotics' activity (Chusri et al., 2009, Khameneh et al., 2019).
Calotropis procera (*C. procera*) is a popular medicinal plant from the family Apocynaceae. It is a xerophytic perennial shrub (or small tree) with stems of 2 to 6 m tall and tap roots 3 to 4 m deep in the soil (Hassan et al., 2015). A thick milky sap or latex exudes out from the plant if its parts are cut or broken (James et al., 2013, Waikar and Srivastava, 2015). *C. procera* grows on a variety of soils and it can tolerate different level of soil salinity, draught stress, intense light of arid and harsh environments. Hence, it is distributed in various tropical and subtropical countries (Hassan et al., 2015).

C. procera has been known as medicinal plant for a long time (Al-Sulaibi et al., 2020), and it has been used in treatment of a diverse array of maladies and particularly infectious diseases (Oraibi and Hamad, 2018, Pathania et al., 2020) Moreover, *C. procera* has been worshiped by ancient Indians and grown near temples (Sharma & Sharma, 1999), used as milk-clothing agent in preparation of the African local cheese called *wagashi* (Belvedere et al., 2010).
Overall information about the medicinal plant *Calotropis procera.[7,8,9]*

Common/vernacular name	Country/Language	Parts used/preparation	Disease
Ushar	Sudan: Arabic	Lt: paste (topical). Lf: powder, decoction, infusion (as mouthwash) or mixed with oil (topical). Fresh Rt: crushed or powdered (topical).	Skin or cutaneous illness: haemorrhoids, skin injuries, and scorpion bits. Rheumatoid pains, mouth infections, jaundice, and asthma.
Ushur, ushar	Yemen: Arabic	Lf: pasted	Skin and dermal illness: skin

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Common/vernacular name	Country/Language	Parts used/preparation	Disease
			infections, boils and scabies.
Akra, Akundia, Akonda or Akond, Akada, Akauwa, Rui, mandara, alaka, ravi, vellerukku,	India: Hindi, Bangali, Marathi, Tamil, Sanskrit	Lf, Rt, RtBk, StBk, Bd, Lt, FL: powdered, pasted, decoction, ashed (topical and oral). Rt: powdered + sugar (orally) RtBk: powdered + honey (orally)	Skin and dermal illness: elephantiasis, wounds, cuts, thorn injuries, inflamed swellings, ulcers, boils, ringworm, leukoderma, and leprosy. GIT illness: helminthiasis, diarrhea, dysentery and cholera. Malaria, fever, pain, jaundice, leucorrhea.
Ushaar, oshar, usher, Kisher,	Saudi Arabi: Arabic	ArPt, FL, Lf, Lt, RtBk, St, Rt: powdered, decoction, liniment, paste (oral and external.	Skin and dermal illness: infections, leprosy, wounds, psoriasis, boils, leishmaniosis, scorpion stings and hair loss. GIT diseases: dysentery, constipation, worms and toothache. Respiratory diseases: bronchial asthma and cough. Malaria, fever, headaches, joint pain, rheumatism, and muscular spasms.
Bunagadhee, Ttobia	Ethiopia	Rt, Lf, Lt: alone or mixed with other plants (topically).	Skin diseases: tropical ulcers, wounds, infections, boils (furuncle).
Al-Ashkar	United Arab Emirates: Arabic	Not specified	External usages to relief inflammations

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Common/vernacular name	Country/Language	Parts used/preparation	Disease
Baniwani, kipanpango	Gambia: Jola language	Lf	Toothache, sore hands
Aldebaj	Iraq: Arabic	Bk: decoction (orally)	Tonic, sudorific, antispasmodic, expectorant, and emetic (large doses)
Flor de seda, ciúme, ciumeira,	Brazil: Portuguese	Lt: as paste (topically)	Skin/dermal diseases: infections
Fogofoko, Anranpobo, Pumpum, Pompo pokolo	Mali	Lf: crushed (topical), decoction (orally and bath)	Headache, muscular pains, pain because of sickle cell disease, malaria
Tumfafiya, Bomubomu and Kayou	Nigeria: Hausa and Yoruba languages	Wp, Lf, St: decoction, ashed, burned or smoked. Lt: fresh paste or with honey	Skin/dermal diseases: eczema, ringworms, fungal infections e.g., *Tinea capitis.* GIT diseases: indigestion, diarrhoea and toothache, Respiratory illness: cough. Fever, rheumatism, rabies (Lt + honey)
Putrepuugu	Burkina Faso	Different parts. Rt: boiled with white stones and cowry shell (decoction as mouthwash)	Neuropsychiatric disorders, liver diseases, malaria, tumour and tooth pain.
Spalmai or Spalmey, Spalmaka, Aak	Pakistan: Pushto, Urdu	Lf: crushed alone or mixed with oil (topically). Lt: mixed with other plants or mustard oil or flour (topically). RtBk, FL, FR, Lf, St, Rt: alone or mixed with other plants. Decoction, infusion, and	Skin/dermal diseases: wounds, scabies, eczema, lice, ringworms, snake and scorpion bites, carbuncle. Respiratory diseases: cold cough, asthma, pneumonia. GIT diseases:

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Common/vernacular name	Country/Language	Parts used/preparation	Disease
		powdered (Oral and topically). Rt: Smoked (inhalation) and ashed.	mouth and dental infections, toothache, cholera, diarrhoea, abdominal pain. UT diseases: kidney stones and chronic renal problems. Jaundice, malaria, fever, earache.
Akondo gach	Bangladesh	Lf: warmed and (topically applied to the painful part of body)	Body pain
NR	Thailand	Lf: grounded and paste (topically)	GIT diseases: aphthous ulcers and lesion
Punpune	Ghana	Rt: poultice (topically)	Skin/dermal diseases: boils
Göbi	Guinea: pular or fula	Lf: decoction (orally)	Malaria
Kebou	Kenya	Lf: ashed (orally) FL: decoction (orally)	Malaria, and as emetic.
Kharak	Iran: Persian	Lf, Lt, Rt: decoction, dressing (topically)	Skin/dermal diseases: inflammations, snake, scorpion and insect bites. Gastric discomforts, and migraine.
Tourjah	Mauritania: local Arabic	Lf: powdered + honey and olive oil (orally).	Respiratory diseases: whooping cough
Tourja	Morocco: Darija	St: decoction (topically)	Skin/dermal diseases: wounds

Abbreviations: Bd; bud, Bk; bark, Lf; leaf, Lt; latex, FL; flowers, FR; fruits, NR; not reported, Rt; roots, RtBk; root bark, St; stem, StBk; stem bark, Wp; whole plant.

C. procera latex (CPL) and its different parts contain various metabolites such as glycosides and cardenolides (Mohamed et al., 2015, Sweidan and Zarga, 2015), flavonoids (Mendki et al., 2005), triterpenoids (Khan et al., 1988, Gupta et al., 2002;), steroids (Khan & Malik, 1989), saponins (Gupta et al., 2002, Gupta et al., 2003), lignans (Abdel-Mageed et al., 2016, Al-Taweel et al., 2017), proteins and different enzymes (Lima-Filho et al., 2010, Kumar et al., 2015, Bezerra et al., 2017, Freitas et al., 2020), hydrocarbons (Erdman & Erdman, 1981), saturated and unsaturated fatty acids (Khanzada et al., 2008, de Sousa et al., 2018).

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C. procera showed a diverse array of biological activities such as antimicrobial (Yesmin et al., 2008, Velmurugan et al., 2012, Tiwari et al., 2016), antidiarrhoeal (Kumar et al., 2001), wound healing (Aderounmua et al., 2013, De Figueiredo et al., 2014), anti-inflammatory (Alencar et al., 2004, Kumar et al., 2011, Ramos et al., 2020), anticancer or cytotoxic (Samy et al., 2012, Mohamed et al., 2015, Chan et al., 2017), *in vivo* immunomodulatory (Nascimento et al., 2016), analgesic (Basu and Nag Chaudhuri, 1991, Pathak and Argal, 2007), anthelmintic (Shivkar and Kumar, 2003, Iqbal et al., 2005), antioxidant (Yesmin et al., 2008), and *in vivo* anti-hyperglycemic (Roy et al., 2005, Rahmatullah et al., 2010a).

Although ethnobotanical uses, phytochemistry and different biological potentials of *C. procera* have been partially reviewed by other authors (Silva et al., 2010, Chan et al., 2016, Chan et al., 2017, Mali et al., 2019, Shamim et al., 2019, Ali-Seyed and Ayesha, 2020, Pathania et al., 2020), there remains the lack of comprehensive review of *C. procera* antimicrobial properties. Therefore, in this review, efforts were made to present a comprehensive and state of the art data regarding antibacterial, antifungal, anti-protozoal and antiviral properties of CPL, its different extracts, fractions and isolated compounds and fungal endophytes which were evaluated for antimicrobial activities. In addition to the compilation of traditional uses of *C. procera* in different countries ,we have also compiled elaborated data regarding antibacterial, antifungal, anti-protozoal, and antiviral activities of CPL and its different crude extracts in tabular forms. The tabulated data including the plant parts, geographical origins, types of extracts, test model, dosage, tested microorganisms. In addition, *C. procera* isolated compounds which have been tested for antimicrobial potential, were also highlighted separately, while future perspective and research opportunities of *C. procera[10,11,12]*

III.RESULTS

C. procera is native to North and Tropical Africa, Western and South Asia and Indochina up to the Arabian Peninsula, and it is widely distributed in Australia, American countries and West indies (Chan et al., 2017, Mutwakil et al., 2017). Being able to grow in both dry and wet environments, the plant develops a wide range of morphological traits, and is found as different morphotypes. The deep and stout taproot system of *C. procera* enable the plant to grow and survive in dry dessert areas (Pompelli et al., 2019). *C. procera* grows in different countries such as Afghanistan, Algeria, Australia, Bangladesh, Bolivia, Brazil, Democratic Republic of Congo, Cameroon, Chad, Chile, China, Colombia, Cuba, Ecuador, Egypt, Eritrea, Ethiopia, Ghana, Guatemala, Guinea-Bissau, Haiti, Jamaica, India, Israel, Jordan, Lebanon, Libyan, Malaysia, Mali, Mauritania, Mexico, Mozambique, Myanmar, Morocco, Nepal, Netherlands Antilles, Nicaragua, Nigeria, Pakistan, Panama, Paraguay, Peru, Puerto Rico, Saudi Arabia, Senegal, Somalia, Sudan, Tanzania, Uganda, United Arab Emirates, Uruguay, Venezuela, Yemen and Zimbabwe (Carruthers et al., 1984, Basu and Nag Chaudhuri, 1991, Mossa et al., 1991, Lev-yadun, 1999, Alencar et al., 2004, Lottermoser, 2011, Breckle et al., 2013, Traore et al., 2013, Azhar et al., 2014, Diarra et al., 2015, Suleiman, 2015, Chandrawat and Sharma, 2016, Meragiaw et al., 2016, Fatima et al., 2018, Al-Fatimi, 2019, Gracia et al., 2019, Shamim et al., 2019, Idm'hand et al., 2020, Yebouk et al., 2020).

Traditional medicinal importance of *C. procera*

C. procera, as an ancient medicinal plant, has been known to Greeco-Arab medicine since long time ago, and ancient Egyptians have used it in Neolithic period in Egypt (Hassan et al., 2015). It is a famous medicinal plant of Ayurveda, Arabic, Siddha, Unani and Sudanese traditional medicines (Sharma and Sharma, 1999, Oraibi and Hamad, 2018, Pathania et al., 2020), and is called by several common and vernacular names such as Giant Indian milked weed, Madar and Sodom apple (English), Ak or Arka (Hindi, Sanskrit), Remiga (Malay), Rubik (Indonesian), Ipekag (Turkish), Oshar or Ushar (Arabic), Kharak (Persian), and Spalmai (Pushto) (Breckle et al., 2013, Parihar and Balekar, 2016, Sadat-Hosseini et al., 2017, Tounekti et al., 2019, Bahadur et al., 2020, Manduzai et al., 2020). In different countries, the CPL and almost all parts of *C. procera* have been used traditionally as multifarious remedies for several medicinal purposes

Different parts of *C. procera* and CPL have been traditionally used by people in different countries (21 countries in total) for treatment of various health problems including tumours, jaundice, body pains, fever, various infections, and so forth (Mascolo et al., 1988, Basu and Nag Chaudhuri, 1991, Sharma and Sharma, 1999, Kumar et al., 2005, Murti et al., 2010, James et al., 2013, Tounekti et al., 2019). It is worth noting that *C. procera* has been used more frequently in treating various infectious diseases that could be broadly classified into five categories of (1). skin and dermal infections (e.g., leprosy, wounds and skin infections, boils, carbuncles, scabies, leishmaniosis, mouth and dental infections), (2) gastro-intestinal tract (GIT) infections (e.g., dysentery, diarrhoea, cholera, gastritis, colitis and worms),

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|| Volume 10, Issue 4, April 2021 ||

| DOI:10.15662/IJAREEIE.2021.1004051 |

(3) respiratory infections (bronchitis, bronchial asthma, cough and pneumonia) and (4) gyneco-urinary infections (chronic renal problems and leucorrhea), and (5) systemic infection (e.g., malaria and elephantiasis).
C. procera has been used both as external (topical) and internal (oral) preparations. However, its external or topical uses were more dominant considering its higher usability in the management of dermal infections, wounds, cuts, wasp stings, psoriasis, eczema, scorpion and snake bites, body pains, and so on .

Toxicity of *C. procera*

Apart from its proven traditional use in various countries , *C. procera* is also enlisted as weed (Gracia et al., 2019), and as a toxic plant (Tossou et al., 2018, Al-Zuhairi et al., 2020). Ingestion of CPL and fresh leaves of *C. procera* by ruminants has caused toxic effects to the animals (Mahmoud et al., 1979a, Mahmoud et al., 1979b). Once the plant was used as abortifacient as well. Toxicity of the plant is principally due to presence of toxic compounds such as toxic cardenolides in its latex and all other parts of the plant.
In addition, *C. procera* grows in all types of soils including roadsides and soils polluted with heavy metals. Since the plant has a high capacity of absorbing various chemicals elements (e.g., heavy metals), it bioaccumulates higher concentrations of hazardous heavy metals such as Cr, Cd, Ni, Pb, etc. and other environmental pollutants in into its different organs/parts. These accumulated heavy metals further contribute to the toxicity of the plant (Naz et al., 2020).
CPL bearing pH 5.2, has a caustic effect on mucosal membranes of the body, while cardiac glycosides of *C. procera*, similar to those of *Digitalis*, coarsely increase heartbeat and subsequently, cause death of the animals (Al-Mezaine et al., 2005, Al-Mezaine et al., 2008).

It is worth noting that CPL caused ocular toxicity while being splashed into human eyes, as several cases in this regard have been documented. For instance, in India (where the plant is worshiped), CPL splashed into the eyes caused ocular toxicity in terms of ocular inflammations, corneal oedema, dimness of vision that might be associated with keratouveitis (Basak et al., 2009, Lakhtakia et al., 2010). Similarly, some cases of permanent endothelial cell injury due to contact and intracorneal penetration of CPL into eyes of some people in Saudi Arabia have been reported (Al-Mezaine et al., 2005, Al-Mezaine et al., 2008). However, owing to its local anesthetic effect on corneal epithelial cells, it is not very painful when CPL is splashed into the eye. Interestingly, CPL is not very toxic to the corneal epithelium, but it is highly toxic to the corneal endothelial cells, causing serious hazards in terms of decrease in endothelial cells count and changes of their morphology (Al-Mezaine et al., 2005, Al-Mezaine et al., 2008).
Toxicity of *C. procera* in experimental animals has also been reported. Arya & Kumar, (2004) reported pro-inflammatory effects of crude CPL and its methanolic extract in experimental animals after being injected with 0.1 mL aqueous solution of the tested samples through sub-plantar injection. Both the dried CPL and its extract revealed inflammatory effects on the paw of animals with a rapid onset and peak effect within the first 2 h following injection. Jato et al., (2010) reported a dose-dependent toxicity of oral administration of aqueous *C. procera* leaf extracts in rabbits. Administration of CPL and ethanolic *C. procera* leaf extract caused significant elevation in level of heart enzymes e.g., creatine kinase-MB isoenzyme (CK-MB), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) in serum along with impairment of the normal structure of heart associated with inflammation and necrosis of cardiac myocytes in experimental animals. Meanwhile, an increase in the malondialdehyde (MDA) level in treated animals' serum was observed. MDA is an index of lipid peroxidation or production of reactive oxygen species (ROS). However, it was found that the toxic effects of CPL and ethanolic *C. procera* leaf extract was dose-dependent (Ahmed et al., 2016). Likewise, nephrotoxicity of *C. procera* fresh leaves (Mahmoud et al., 1979b), CPL and ethanolic *C. procera* leaf extract has been reported through *in vivo* study (Fahim et al., 2016).
Interestingly, in another *in vivo* study it was found that CPL toxicity was related to the rubber (>90% in crude CPL) portion and other organic fractions of the latex. The rubber-free or purified water-soluble proteins of CPL was nontoxic to the animals even at high oral dose of 5000 mg/kg/bw (Bezerra et al., 2017).
C. procera wildly grows in many countries and is traditionally used for diverse medicinal purposes, as well. However, topical or external use of the plant seems to be somehow safer when compared to oral use of the plant. Meanwhile, caution is required to avoid direct contact of CPL and other herbal preparations of the plant with the eyes.[13,14,15]
Overall, toxicity of *C. procera* local herbal preparations should not be ignored, and it is recommended to be cautiously used as per advice of qualified traditional community healers or herbal medicine experts.

Antimicrobial activities of *C. procera*

Microbial diseases are caused by any of the four common types of microorganisms which include bacteria, fungi, protozoa and viruses. Many MPs including *C. procera* have been traditionally used as natural antimicrobial remedies in

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|| Volume 10, Issue 4, April 2021 ||

| DOI:10.15662/IJAREEIE.2021.1004051 |

treatment of various infections caused by the pathogenenic microorganisms (Joshi, 2018). As per the literature survey, *in vitro* antimicrobial potentials of *C. procera* have been investigated against a wide range of microorganisms, which are discussed below under four sub-headings specified for antibacterial, antifungal, anti-plasmodial, and antiviral activities of *C. procera*. For ease of understanding and reading, the data are shown in tabulated forms that includes the used plant parts, geographical origin, solvents and extracts' types, test model, dosage, test microorganisms along with their ATCC or NTCC numbers, the brief results and references.

Antibacterial activity of *C. procera* latex and extracts/fractions of different parts

The CPL and different parts of *C. procera* collected from several countries and geographical origins have been investigated for antibacterial properties against numerous Gram-negative (G+ve) and Gram-positive (G–ve) bacterial strains (Mascolo et al., 1988, Yesmin et al., 2008, Nenaah, 2013a, Tiwari et al., 2016, Radwan et al., 2019). About 57 original publications on antibacterial effects of *C. procera* were reviewed and their summarised results As different parts/products of *C. procera* e.g., arial parts, buds, flowers, fruits, latex (CPL), leaves, roots, root-bark, seeds, stems/twigs, stem-barks and whole plant have been tested *in vitro* against over 65 different bacterial strains. The dominant plant parts that have been tested for antibacterial activity (study case) were the leaves (37 study cases), followed by flowers (14 cases), roots (11 cases), stems (9 cases), CPL (8 cases), fruits (3 cases), stem-barks (3 cases), and the remaining parts with only one study case for each. In few cases, extracts prepared from *C. procera* endophytes also showed antibacterial properties (Aharwal et al., 2014, Rani et al., 2017). Wells' diffusion method (WDM) and disc diffusion method (DDM) were the two commonly used antibacterial assay methods, while Micro-dilution method (MDM), tube dilution method (TDM) and time kill assay (TKA) were also used by some authors. Different authors used various solvents extracts and varied dose ranges (0.01–25 mg/well) in *in vitro* antibacterial assay, and consequently diverse levels of antibacterial potency of *C. procera* different parts and CPL were reported. For instance, in some studies, aqueous extract of *C. procera* showed potent antibacterial effects (Yesmin et al., 2008, Samy and Chow, 2012, Panda, 2014), while in another study the aqueous extract of *C. procera* was the least active sample (Parabia et al., 2008, Asfere et al., 2018). Some authors reported methanolic and ethanolic extracts of the plant with good potency (Salem et al., 2014, Kar et al., 2018), while others reported nonpolar fractions of other organic solvents extracts of *C. procera* as potent samples (Morsy et al., 2016). In certain cases, the EtAc extracts were the most potent samples (Mohanraj et al., 2010). Similarly, some authors reported CPL extracts with potent antibacterial effects (Kareem et al., 2008), while in another study, CPL did not show antibacterial effects (Jain et al., 1996). Unfortunately, some authors did not clearly mention the doses used in WDM or DDM of *in vitro* antibacterial assay (Adamu et al., 2005, Oladimeji et al., 2006, Mainasara et al., 2011, Mainasara et al., 2012).

Overall, due to experimental inconsistencies, comparison of the results of *C. procera* antibacterial studies seems to be very complicated. However, more systematic and in-dept studies are encouraged to explore antibacterial potential of *C. procera* isolated compounds and their MOA that hopefully serve as new antibacterial agent (s).

Antifungal activity of *C. procera* latex and extracts of different parts

In vitro antifungal activity of CPL and extracts of different parts from *C. procera* against numerous fungi and yeasts have been evaluated by several researchers. As per about 23 reviewed literatures, different extracts of *C. procera* and of its CPL have been tested for *in vitro* antifungal potential against different fungi and yeasts. In this regard, for ease of reading the summarized data extracted from reviewed literatures are presented in tabular forms . As shown CPL and extracts of different parts e.g., arial parts, flowers, fruits, leaves, roots, rootbarks, stems, and stem-barks of *C. procera* were reported for their *in vitro* antifungal effects against around 27 different fungi and yeasts. With regards to antifungal study of *C. procera*, its leaves were the dominant plant part (14 study cases), followed by CPL (7 cases), stems (4 cases), flowers (3 cases), roots (2 cases), stem-barks (2 cases), and only one study case for each of *C. procera* aerial parts and fruits. In a study, 35 fungal endophytes isolated from *C. procera* leaves were tested for their antifungal potential and six of them was active against some tested fungi (Nascimento et al., 2015).

Various authors used different solvent extracts and diverse dose ranges (0.005–5 mg/well) in *in vitro* antifungal assay of the test samples. Dissimilarities are obvious in the reported results of the studies. For example, aqueous extracts of *C. procera* leaves, stem barks and roots significantly inhibited (97.80%) the growth of tested fungi (Hassan et al., 2006). In another study, EtAc extract of leaves showed stronger antifungal effects when compared to other extracts (Halu & Vidyasagar, 2012), while CHL: MeOH (5:1) fraction of crude EtOH leaf extract of *C. procera* produced larger ZOI (up to 19 mm) when compared to that of the crude EtOH leaf extract (Verma et al., 2012). Nenaah & Ahmed, (2015) found that yeasts were more susceptible than mycelial fungi to both aqueous and MeOH extracts of *C. procera* leaves, flowers and CPL. However, in this study, MeOH extracts were more potent against the tested fungi[16,17,18] (Nenaah & Ahmed, 2015). Interestingly, crude CPL at doses of 5–30 µg/wells was not active against *C.*

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|| Volume 10, Issue 4, April 2021 ||

| DOI:10.15662/IJAREEIE.2021.1004051 |

albicans and *A. niger*, while EtOH and aqueous extracts of dried CPL serum 2.5–12.5 µg/wells elicited antifungal effects (ZOI up to 16 mm) against the tested fungi (Hassan et al., 2017).
Indeed, there are considerable controversy also in results of previously reported antifungal studies, and hence, comparison of the results of different works would be difficult.

2.3. Antiprotozoal activities *C. procera*

To justify the traditional uses of *C. procera* as anti-malarial remedy, some authors have investigated *in vitro* and *ex vivo* anti-plasmodial effects of the plant against *Plasmodium* species (Sharma and Sharma, 2000, Simonsen et al., 2001, Mudi and Bukar, 2011, Muthaura et al., 2015, Singh et al., 2015). In addition, antileishmanial property of *C. procera* has also been recently reported (Nasr, 2020). The antiprotozoal properties of CPL and extracts of different parts of *C. procera*. Both flowers and leaves of *C. procera* were the dominant plant parts with 4 and 3 study cases, respectively, in antiplasmodial studies of the plant against different *Plasmodium* species. Buds, roots, whole plant and stems of *C. procera* were also studied against *Plasmodium* species but CPL is still not evaluated for anti-plasmodial or anti-protozoal potential. As shown *C. procera* leaves EtOH extract revealed a strong *ex vivo* anti-plasmodial effect with IC_{50} of 2.5 and 2.9 µg/mL against chloroquine-sensitive (P*f*3D7) and chloroquine-resistant (P*f*INDO) *Plasmodium falciparum*, respectively. In this study, *C. procera* was one the most potent plants among 22 medicinal plants used traditionally for treatment of malaria in Jharkhand, India (Singh et al., 2015).
Although *C. procera* has been traditionally used in treatment of cutaneous and digestive illnesses, more recently, a dose-dependent *in vitro* antileishmanial potential of *C. procera* leaves was reported (Nasr, 2020). In this regard, studying antiprotozoal properties of *C. procera* against other protozoa particularly responsible for digestive illnesses would be interesting research topics. Considering traditional uses of *C. procera* in alleviating digestive system upsets, anthelminthic properties of this plant have already been established through *in vitro* (Shivkar & Kumar, 2003) and *in vivo* studies (Iqbal et al., 2005).

2.4. Antiviral activity of *C. procera*

Viral diseases are considered as one of the major threats for human, animals and plants globally. In addition to the challenges due to emergence of antiviral resistance and also side effects of available antiviral drugs (Bagla et al., 2012), the outbreaks of deadly viral diseases such COVID-19 which is severely challenging human survival worldwide further necessitates the discovery of vaccines or treatment solutions against these deadly microorganisms.
MPs have been proven to contain bioactive compounds with antiviral properties, and some of them have shown promising and broad spectrum antiviral potentials (Mukhtar et al., 2008, Mohanraj et al., 2010, Tariq et al., 2019). As per literature, *C. procera* has also been investigated for its *in vitro* and *in vivo* antiviral effects (Khurana and Singh, 1972, Mohanraj et al., 2010, Saher et al., 2018, Velmurugan et al., 2012), as summarised
Data in Table 5 indicates that the antiviral properties of CPL and other extracts of *C. procera* seem to be promising despite the limited studies that reported the antiviral potential of *C. procera* against only four viral species. Hence, further in-depth studies are required in order to isolate potent antiviral compounds from this miracle plant.
It would be difficult to compare reported results of different works. For instance, some studies reported good antibacterial potential of the nonpolar fractions of *C. procera* extracts (Morsy et al., 2016), while some others reported methanolic extracts of the plant with higher *in vitro* antibacterial properties (Kar et al., 2018). However, such controversies in the results of biological screening of crude plant extracts could be attributed to several factors such as: geographical origin of raw materials, time of sample collection, nature or types of solvents used in the extraction, extraction procedures, purity of extracts, dose ranges, diversity in genetics of test microorganisms, assay methods, etc. (Muthaura et al., 2015).

Interestingly, from around 78 original research that had reported the antimicrobial properties of *C. procera* 35 (44.87%) of them have been conducted on raw materials collected from different parts of India, followed by Nigeria with 14 studies (17.94%), Saudi Arabia with 7 studies (8.97%), Pakistan with 7 studies (8.97%), Egypt with 6 studies (7.69%), Ethiopia with 2 studies (2.56%), and Bangladesh, Brazil, Kenya, Morocco, Iraq, United Arab Emirates and Yemen each with one study (1.28%).
Briefly, current review showed that, *C. procera* from about thirteen different countries have been collected and studied for different antimicrobial (antibacterial, antifungal, antiprotozoal and antiviral) activities by various groups of researchers. On the other hand, it was found that researchers had screened *C. procera* against different categories of microorganisms of human, animal and plant pathogens since 1980. Meanwhile, as per the overall data shown in to date *C. procera* is being screened *in vitro* against >90 different microbial strains including 34 G–ve bacteria, 31 G+ve

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|| Volume 10, Issue 4, April 2021 ||

| DOI:10.15662/IJAREEIE.2021.1004051 |

and 2 g-variable pathogens, 27 fungal strains, 6 protozoa (including both chloroquine sensitive- and chloroquine-resistant *P. falciparum* and *Leishmania major*), and 4 viral pathogens[19]

IV.CONCLUSION

Calotropis procera is a commonly used herb in Ayurvedic medicine. This review supports all updated information on its phytochemical and pharmacological activities, traditional uses and scientific approach. The plant extracts and its chemical marker or target molecule Arecoline have been widely used for the treatment of a large number of human ailments. The chemical entities of this plant has been used as an antidiabetic, blood pressure regulating activity, antiulceogenic, antioxidant activity, anticonvulsant activity, C.N.S. stimulant activity, oxytocic activity, antifertility, anthelmintic and antiviral activity etc. Scientifically proved activities are related with traditional concept. Scientific evidence exists with respect to their major and minor constituents.[20]

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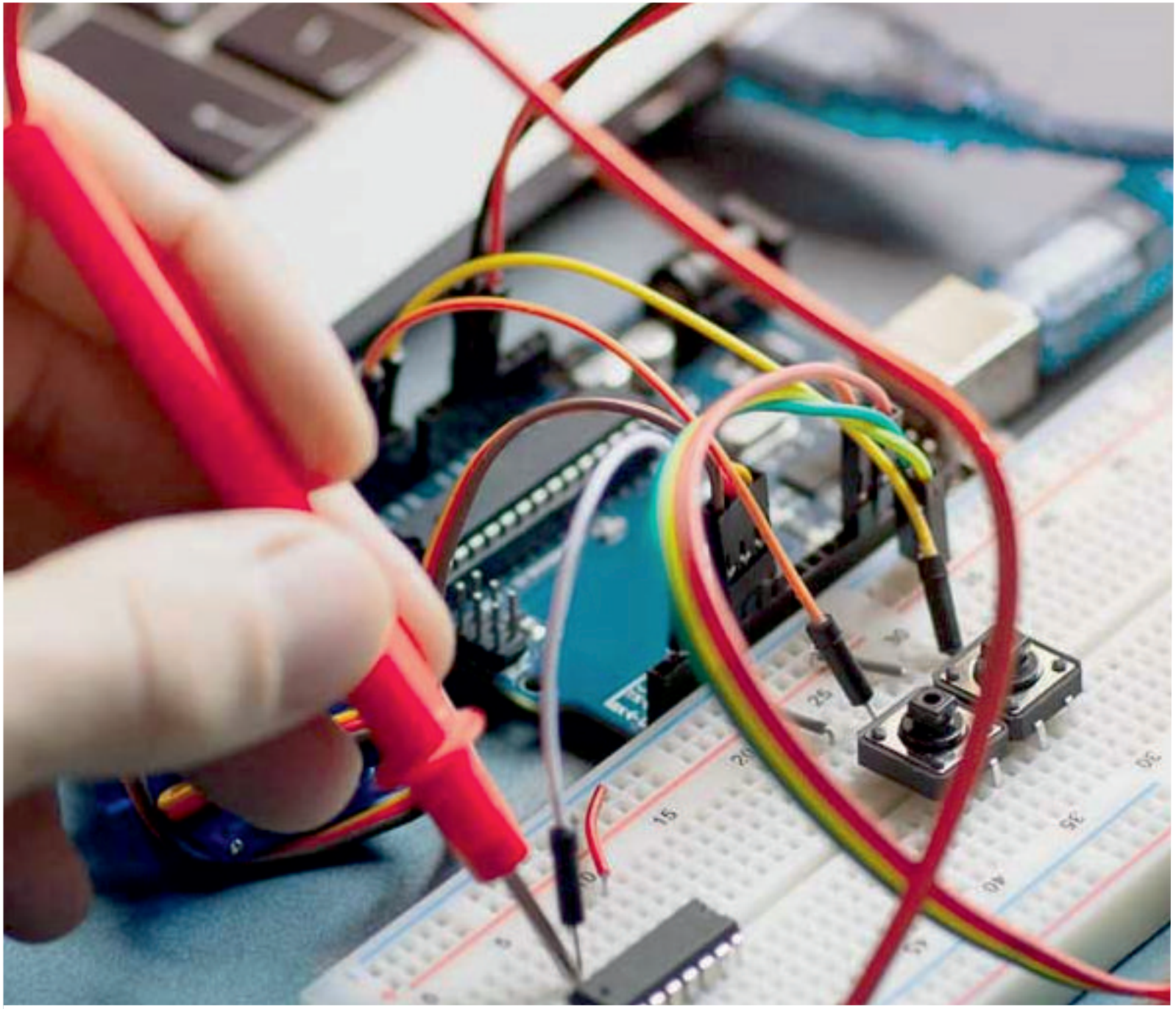

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