Annals of Phytomedicine 13(2): 44-54, 2024

DOI: http://dx.doi.org/10.54085/ap.2024.13.2.5

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

Biological activities and diabetic wound healing potential of *Couroupita guianensis* Aubl. flowers: Current knowledge and concepts

Santwana Palai◆, Sk Abdul Rashid, Ritun Patra*, Sarita Jena, Biswakanth Kar***, Sabitri Bindhani*** and Kautuk Kumar Sardar**

Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar-751003, Odisha, India

** Department of Veterinary Anatomy and Histology, College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar-751003, Odisha, India*

*** Experimental Animal Facility, Institute of Life Sciences, Bhubaneswar-751023, Odisha, India*

**** School of Pharmaceutical Sciences, Siksha O Anusandhan, Deemed to be University, Bhubaneswar-751030, Odisha, India*

Article Info

Article history

Received 17 August 2024

Revised 3 October 2024

Accepted 4 October 2024

Published Online 30 December 2024

Keywords

Cannonball tree

Antioxidant

Antimicrobial

Wound healing

Antidiabetic

Anti-inflammatory

Abstract

Diabetic wounds are significantly difficult to manage in a clinical context because they heal slowly and can persist for weeks. The highly oxidizing environment linked to hyperglycemia and tissue hypoxia causes delayed wound healing. Due to their therapeutic effect, medicinal plants have long been used to treat human illnesses. The pink, red, and yellow colored originally peri-Amazonian *Couroupita guianensis* Aubl. (cannonball tree) flowers have snake hood-like structures and are used for Shiva prayer in India. This tree is extremely beneficial in treating a variety of illnesses, being rich in active secondary metabolites. The flowers of *C. guianensis* exhibit antitumor, antidiabetic, and hypocholesterolemic effects. It also has an antioxidant effect which can be effective in the highly oxidizing environment of diabetic wounds. Its antibacterial and antifungal effects can act against bacteria like *Escherichia coli, Staphylococcus aureus, Pseudomonas species,* and fungi like *Candida albicans,* respectively, where the microbes aggravate diabetic wounds, resulting in delayed healing. Owing to its many bioactive components having antioxidant, antimicrobial, anticancer, antiarthritic, anti-inflammatory, antiulcer, and immunomodulatory effects, *C. guianensis* is; therefore, a possible source of novel drugs that can heal diabetic wounds. Further investigations can be done on the contribution of *C. guianensis* flowers in the healing process of impaired diabetic wounds to establish it as an alternative therapeutic for diabetic wounds.

1. Introduction

Diabetes mellitus is a multi-factorial illness caused by impaired insulin production or glucose sensing, autoimmune-mediated β-cell death in type 1 diabetes, or an inadequate response to local insulin resistance in type 2 diabetes (Meur *et al*., 2024). In diabetes, uncontrolled glucose regulation and increased protein glycosylation are mostly attributed to hyperglycemia, whereas glucose oxidation generates free radicals that harm cellular membranes by oxidizing low-density lipoproteins (Papachristoforou *et al*., 2020). Two dangerous complications of diabetes are hyperglycemia and dyslipidemia, which lead to the development of many secondary illnesses like diabetic wounds. Diabetic wounds are a clinically significant consequence of diabetes, with an increasing global population of diabetics. China and India have some of the highest rates of diabetic wounds; due to socioeconomic factors associated with their expanding economies, which have accelerated the development of lifestyle disorders. 50% of diabetic people in India develop diabetic wounds and require hospitalization, and 20% require amputation (Ghosh and Valia, 2017). The frequency of diabetic foot ulcers in China varies from 17.03% to 42.84% which is significantly greater than in other nations (Zhang *et al*., 2024).

Diabetic wounds are significantly difficult to manage in a clinical context because they heal slowly and are challenging to maintain as they can persist for weeks. It is unclear exactly which pathophysiology leads to poor wound healing in diabetic wounds (Burgess *et al*., 2021). Diabetic foot is a complication involving persistent sores that do not heal and often result in limb amputations, which leave the patient incapacitated and with a reduced quality of life. This lowers the patient's quality of life and necessitates expensive therapies. Therefore, it is essential for the creation of fresh, potent treatment approaches for this condition (Burgess *et al*., 2021).

Plant bioactive substances such as flavonoids, glycosides, mucilage, saponins, steroids, and resins are involved in the process of healing (Patel *et al*., 2019; Palai *et al*., 2023) because these parts contain phytochemicals with antimicrobial, antiviral, antioxidant, antibacterial, anti-inflammatory like pharmacological properties (Al-Dhabi *et al*., 2012; Palai and Patra, 2021).

Couroupita guianensis Aubl. (cannonball tree) is a big, beautiful, and tall deciduous flowering tree. Traditionally *C. guianensis* flower is used in scabies, dysentery, piles, hemorrhage, and scorpion

Corresponding author: Dr. Santwana Palai

Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Odisha University of Agriculture and Technology, Bhubaneswar-751003, Odisha, India

E-mail: santwanap@ouat.ac.in

Tel.: +91-9438298384

poisoning (Shah *et al*., 2012) and its leaves and mature flowers are used in stomach upset, tumors, pain, and inflammatory processes (Sanz-Biset *et al*., 2009). This review article focuses on the plant chemicals of *C. guianensis* flower that have the potential to be beneficial for diabetic wounds, as they tend to have less adverse effects, multifaceted mechanisms, and a longer duration of action.

2. Pathophysiology of diabetic wound healing

Diabetes affects wound healing for a variety of reasons which are both internal and external to the wound. Extrinsic variables include ischemia brought on by macro or microvascular illness, as well as recurrent trauma or mechanical stress given to an organ, such as the foot, that has rendered insensitivity by neuropathy. Diabetes usually results in thicker capillaries and arteriole basement membranes, which decelerates wound healing and extends the development of ulcers. One of the primary causes of chronic wounds in people with diabetes is hyperglycemia, which hinders wound healing by forming AGEs that stimulate the release of inflammatory molecules like TNF-α and IL-1 and disrupt collagen synthesis. Also, exposure to elevated glucose is linked to alterations in cellular morphology, reduced keratinocyte proliferation, and aberrant keratinocyte differentiation that impair diabetic wound healing. Diabetic patients with lower HbA1c have shorter healing duration for leg and foot ulcers, demonstrating the link between hyperglycemia and poor wound healing (Shaikh Kader *et al*., 2019).

Patients with diabetes may also experience impaired wound healing due to decreased immune function. The early stages of wound healing in diabetes have been linked to decreased heat shock protein expression, phagocytosis, chemotaxis, and bacterial death. Changes in leukocyte infiltration and the presence of IL-6 in the wound fluid are indicative of the late inflammatory phases of wound healing in individuals with diabetes. Thus, the pathophysiology of chronic wounds has been linked to altered patterns of expression of cytokines and growth factors (Figure 1).

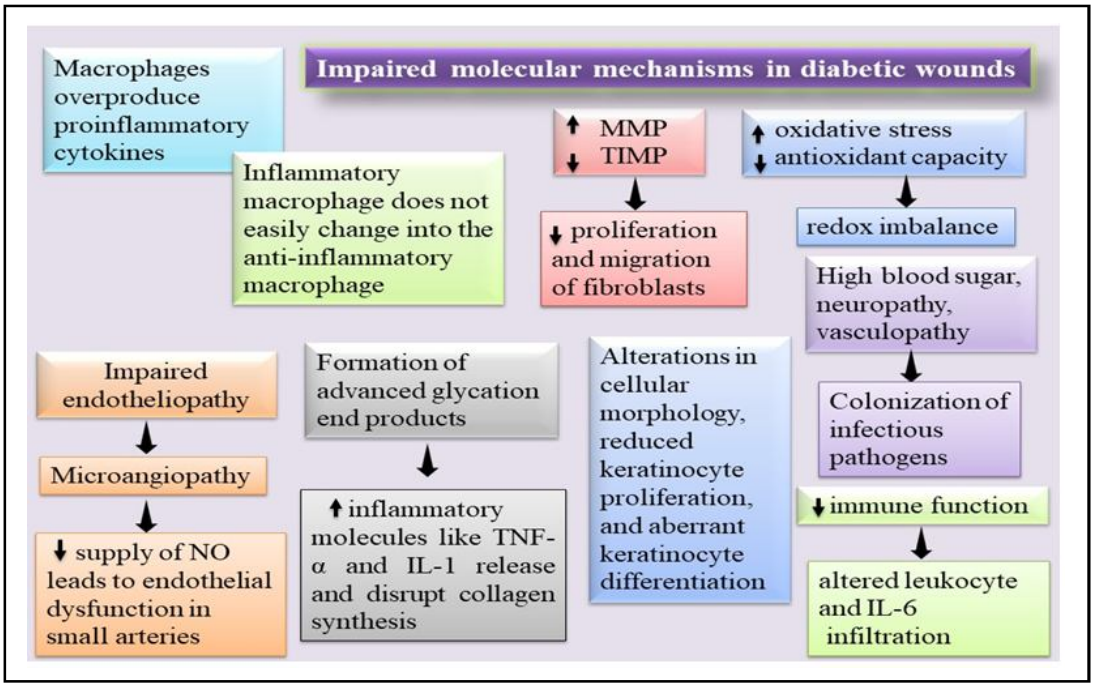

Figure 1: Impaired molecular mechanisms in non-healing diabetic wounds.

3. Cells and signaling chemicals closely linked to the diabetic wound's inability to heal

Hyperglycemic condition is the main cause of impaired wound healing in diabetic wounds. Diabetic wounds heal more slowly during the inflammatory phase than non-diabetic wounds. This prolonged pro-inflammatory state impairs wound healing and can lead to the development of a chronic wound. Different cell types release signaling chemicals to regulate the motility, metabolism, proliferation, and differentiation of cells. The healing process may be hampered by certain macromolecules like albumin, fibrinogen, and β2-macroglobulin entangling growth factors and cytokines (Berry-Kilgour *et al*., 2021). Phagocytic and pro-inflammatory macrophages are the first to appear during the inflammatory phase of normal wound healing. Eventually, ECM-producing, anti-inflammatory macrophages that stimulate angiogenesis take their place (Davis *et al*., 2018). Macrophages overproduce pro-inflammatory cytokines in diabetic wounds. Furthermore, in diabetic wounds, the inflammatory macrophage does not easily change into the anti-inflammatory macrophage as happens in normal wounds (Boniakowski *et al*., 2017).

Additionally, the balance between the buildup of extracellular matrix components that are collagenous and non-collagenous is necessary for optimal wound healing. Tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs) control their remodeling. MMPs are crucial for angiogenesis, epithelialization, and the remodeling of scar tissue in addition to the initial debridement of wounds. Individuals with diabetes mellitus have wounds with higher MMP and lower TIMP levels. Finally, phenotypic alterations in resident cells of chronic wounds may hinder their ability to proliferate and migrate. For example, fibroblasts from pressure and venous

ulcers are aged with a reduced capacity to divide, and the incapability to divide is closely related to the wound's inability to heal (Pastar *et al*., 2024).

Endotheliopathy is impacted by hyperglycemia via pathways that result in microangiopathy, including hexosamine, polyol, AGEs, and PKC pathways. The PKC pathway appears to have the greatest direct impact on endothelial vascular dysregulation among these four pathways. Hyperglycemia can either directly or indirectly enhance the synthesis of PKC family regulating enzymes or DAG. By activation of these pathways, micro arterioles that control the smooth muscle contractility of the arteries supplying distant tissue areas malfunction in a way that is dependent on the endothelium. Furthermore, suppression of the NO and EDHF pathways, as well as increased production of endothelin-1 and oxygen-free radicals, lead to endothelial dysfunction in small arteries (Mieczkowski *et al*., 2022).

4. Redox imbalance in diabetic wounds

The redox imbalance is a significant contributing factor to diabetic wounds that do not heal due to increased oxidative stress on tissues and a reduction in antioxidant capacity (Palai *et al*., 2023). The polyol pathway lowers cytosolic NADPH, which inhibits the production of oxygen free radicals and neutralizes endotheliopathy resulting from the reduced supply of nitric oxide in malfunctioning arteries. DNA damage is mediated by endothelial cell malfunction, which is exacerbated by the production of ROS products. Low ROS levels are necessary for the defense against external damage (Checa and Aran, 2020). However, redox imbalance which is brought on by elevated oxidative stress on tissues and a decline in antioxidant capacity is the major contributing factor to diabetic wounds that do not heal. The highly oxidizing environment delays wound healing and is associated with hyperglycemia and tissue hypoxia (Nirenjen *et al*., 2023, Deng *et al*., 2021).

5. Microbes aggravating diabetic wounds

Gram-positive bacteria like *Enterococcus* species and *S. aureus* as well as gram-negative bacteria like *E. coli, P. aeruginosa, Klebsiella* species*, Proteus* species*, etc.,* and anaerobes, are abundantly found in diabetic ulcers (≥6 log CFU/ml) (Ishwarya and Neelusree, 2019). Many antibacterial drugs are available to treat infection, however, the potential for microbes to develop multidrug resistance can outweigh the benefits of a whole class of antibacterial drugs. As a result, the hunt for fresh, secure, and efficient antibacterial agents is essential (Terreni *et al*., 2021).

In patients with diabetes, inflammatory skin illnesses and fungal foot infections such as *Tinea pedis* and onychomycosis are considerably more frequent than the general population (Aragón *et al*., 2023). High blood sugar, neuropathy, vasculopathy, and other immunological disorders are predisposing variables that create an environment that is favorable to the colonization of pathogenic fungi, such as *Aspergillus, Candida* species, *Dermatophytes, Malassezia, Mucorales,* and *Fusarium* species. Infections caused by these pathogens like myiasis might result in delayed wound healing or even patient mortality due to disturbance in the immune system and skin integrity as well as inadequate self-care (Ozturk *et al*., 2019).

6. Standard treatment methods for diabetic wounds

Diabetic ulcers are typically treated with a combination of techniques such as extensive debridement, antibiotic therapy based on cultures of wound pathogen, offloading high pressure from the wound bed, moisture dressings, and measures to optimize glycemic control and vascular status. To facilitate secondary wound healing, surgical debridement is used for removing necrotic, devitalized wound bed and edge tissue which impedes the healing of diabetic foot ulcers. By culturing suitably obtained tissue specimens to identify the organisms causing a diabetic foot infection, physicians can select the best antibiotics based on culture and sensitivity findings. When treating diabetic foot ulcers, different forms of wound dressings should consider the qualities of the wound as well as the dressing cost. There are now only a few FDA-approved therapies and equipment in the market, including Omni graft, cell-based therapy, collagenase ointments, PDGF-BB growth factor, and shock wave therapy. These choices are symptomatic and either have a short half-life or reduced efficacy and negative effects. Therefore, there is not a suitable, generic medication that can treat diabetic wounds (Tsourdi *et al.,* 2013) (Figure 2).

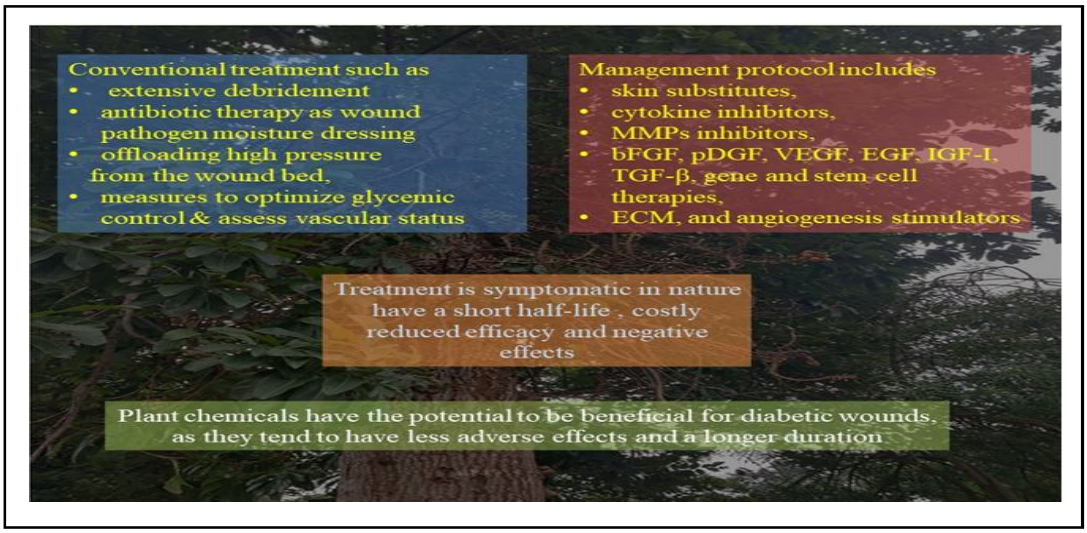

Figure 2: Treatments of diabetic wounds.

7. Potential of *C. guianensis* flowers

Plants are frequently used whole or in parts like leaves, roots, stems, flowers, and seeds in wound care (Sheba *et al*., 2023). *C. guianensis* is a big, beautiful, tall deciduous flowering tree found in Indian gardens because of its lovely blossoms and aroma belonging to the family Lecythidaceae. Originally, belonging to the tropical forests of Central and South America, it is mostly distributed in the vicinity of the Amazon Basin in South America. It is also cultivated in other tropical areas globally because of its fragrant flowers and large brownish-grey fruits. It has religious, cultural, and medicinal significance throughout South and Southeast Asia. Its zygomorphic flowers have a strong scent with six mostly pink, red, and yellow-tinged petals. The stamens are present centrally in the form of a ring as an overhanging androphore (Figure 3). Its large, globose fruits with woody shells dangle in clusters like balls on a thread (Aravind *et al*., 2017). Because of the resemblance of the Shivalingam form in the center of the blossom and the pollens resembling snake hoods, these trees are typically planted on the premises of Shiva temples in India and used for worshiping Shiva (Sundararajan and Koduru, 2014). *C. guianensis* flower shows analgesic, anti-inflammatory, immunomodulatory, anthelmintic, antibacterial, wound-healing, antioxidant, and antinociceptive properties (Bhagyasri *et al*., 2014).

Figure 3: ***C. guianensis*** **flower (a), petals (b), and tree (c).**

7.1 Phytochemical analysis of *C. guianensis* flower extracts

In some previous studies, *C. guianensis* flower extraction was done using numerous solvents like methanol, pet-ether, ethanol, ethyl acetate, chloroform, and water of which ethyl acetate showed maximum yield (25.3%) and qualitative analysis for ethnopharmacological studies through chemical test were performed which distinctive the presence of flavonoids, triterpenes, alkaloids, steroids, proteins, phenols, glycoside, tannins, saponins, *etc*. (Shwetha *et al*., 2020). The ethyl acetate fraction of aqueous *C. guianensis* flower extracts showed better antioxidant effects and the methanolic extract showed better antimicrobial, anxiolytic, and immunomodulatory effects. The chemical studies of *C. guianensis* flower have shown the presence of α-amirin, β-sitosterol, indirubin, isatin, nerol, β-amirin, tryptanthrine, linoleic acid, indigo, carotenoids, and sterols (Table 1).

Table 1: Phytochemicals present in *C. guianensis* flower with their pharmacological effects

S. No.	Phytochemicals found in *C. guianensis* flower	Pharmacological effect that aid in wound healing	Reference
1	Myristoleic acid	Cytotoxic and apoptosis-inducing effects	Prabhu *et al*., 2015
2.	Linoleic acid	Lowers cholesterol, and high blood pressure, reverses atherosclerosis	Prabhu *et al*., 2015
3.	Amirin	Antinociceptive, anti-inflammatory, and antioxidant effects	Prajapati and Tiwari, 2022
4.	β-sitosterol	Antihyperlipidemic, anticancer, antioxidant agent	Prajapati and Tiwari, 2022
5.	2',4'-dihydroxy-6'-methoxy -3',5'-dimethylchalcone	Anticancer and antioxidant agent	Prajapati and Tiwari, 2022

6.	7-hydroxy-5-methoxy-6,8 -dimethylflavanone	Anticancer and antioxidant agent	Prajapati and Tiwari, 2022
7.	4-hydroxybenzoic acid	Antioxidant effects, fungicides	Prajapati and Tiwari, 2022
8.	Isatin	Antitumor effect	Tripathi and Sonawane, 2013
9.	Indirubin	Anticancer effect	Prajapati and Tiwari, 2022
10.	Eugenol	Antioxidant, anti-inflammatory, and cardioprotective properties	Gupta *et al*., 2012
11.	Linalool	Analgesic, anti-inflammatory, antitumor, antibacterial effects	Gupta *et al*., 2012
12.	Farnesol	Antimicrobial, and antitumor effects	Gupta *et al*., 2012
13.	Nerol	Antimicrobial effects	Gupta *et al*., 2012
14.	Vanillin	Antioxidant and anti-inflammatory effects	Gupta *et al*., 2012
15.	Limonene	Antioxidant effect	Wong and Tie, 1995
16.	Geranial	Anti-inflammatory, antibacterial, antioxidant antiparasitic, anti-cancer, antifungal, antinociceptive activities	Wong and Tie, 1995
17.	Ocimene	Antioxidant effect	Wong and Tie, 1995
18.	Nootkatone	Anti-inflammatory, anticancer, and mild antimicrobial effect	Wong and Tie, 1995
19.	Geraniol	Antifungal, antibacterial effect	Tripathi and Sonawane, 2013
20.	2-isopropenyl-5-methylhex -4-enyl acetate	Antimicrobial and anti-inflammatory effects	Tripathi and Sonawane, 2013
21.	Cedr-8- en-13-ol	Antifungal, antibacterial, anticancer, and have mild hypotensive effect	Tripathi and Sonawane, 2013
22.	Farnesyl acetate	Antimicrobial, anti-inflammatory, and antioxidant effects	Tripathi and Sonawane, 2013
23.	Methyl (11E)-11-hexadecenoate	Antimicrobial, and antioxidant effects	Sheba and Anuradha, 2019
24.	Cycloset-24-en 3-ol-3'-exomethylene heptadecanoate	Anticancer, and antioxidant effects	Sheba and Anuradha, 2019
25.	Stigmasterol acetate	Anticancer, anti-inflammatory, antiarthritic effects	Sheba and Anuradha, 2019
26.	Coumaric acid	Antioxidant, antiulcer, antimicrobial, antiarthritic, cardio-protective, hepatoprotective effects	Sheba and Anuradha, 2019
27.	Caffeic acid	Anticancer and antioxidant effects	Sheba and Anuradha, 2019
28.	Quercetin	Antibacterial, antioxidant, protein kinase inhibitor, phytoestrogen, radical scavenger	Sheba and Anuradha, 2019
29.	Swietenine	Anti-inflammatory property	Landge, 2021
30.	Sapropterin	Liver cirrhosis and portal hypertension	Landge, 2021
31.	Usnic acid	Anticancer effects	Landge, 2021
32.	Lupeol	Antioxidants, anti-inflammatory, and antimutagenic effects	Landge, 2021
33.	Gamma tocopherol	Antioxidant effect	Landge, 2021

7.2 Wound healing activities of *C. guianensis* flower

The alcoholic extract of *C. guianensis* contains flavonoids and stigmasterol which greatly aids in wound contraction. Thus, by reducing the surface area of the wound and hovering its tensile strength, *C. guianensis* fastens up the healing process (Swapnalatha and Rajeswari, 2014). Also, *C. guianensis* flowers can serve as alternative treatments in angiogenesis and proliferative phase of diabetic wounds owing to their antioxidant, anti-inflammatory (Singh *et al*., 2015), antibacterial, and antifungal (Kumar and Yadav, 2022) like effects (Figure 4).

7.3 Antioxidant activity of *C. guianensis* flower

The aqueous extract of *C. guianensis*'s ethyl acetate fraction has strong *in vitro* antioxidant activities (Bafna *et al*., 2011) as examined through the DPPH assay. It influences reducing power, superoxide scavenging, and *in vitro* lipid peroxidation showing its *in vitro* inhibiting activity. The results show that the ester fraction of the *C. guianensis* water extract was much more efficient than the superoxide radical (EC_{50}: 10.65 µg/ml) and DPPH (EC_{50}: 24.41 µg/ml) in scavenging it (Sundararajan and Koduru, 2014). In comparison to ascorbic acid (standard), with 0.05 ± 0.014 AAEq mg/ml extract, the greatest antioxidant activity was recorded for the MeOH extract of petals, which was 2.98 ± 0.245 AAEq mg/ml of extract (Rokkam *et al*., 2023).

Senadeera and Udukala (2023) noted that *C. guianensis* flower methanolic extract has a higher EC_{50} value (623 mg/l) than a standard ascorbic acid (41 mg/l) through the DPPH assay. Also, AgNPs synthesized from the *C. guianensis* flower exhibited a better antioxidant effect in comparison to the antioxidant potential of the *C. guianensis* flower extract (Babu *et al*., 2022). These AgNPs had 70.35% antioxidant activity at 20% of the sample concentration, compared to just 28.50% in floral extract (Singh *et al*., 2021).

A study on the antioxidant profile of *C. guianensis* using hydrogen peroxide-treated goat liver slices as an *in vivo* simulated *in vitro* system revealed that the alkaloid and methanolic extract of the flower sample have effective antioxidant activity in comparison to the leaf extract. Groups administered with flower extracts showed significant increases in enzymatic (SOD, CAT, POD, GST, GPx) and non-enzymatic (vitamins A, C, and E and GSH) antioxidant activities as compared to methanolic extract (Kavitha *et al*., 2024). As a result, it is found that flower samples are superior to leaf extracts in scavenging free radicals.

Phytochemicals such as flavonoids, terpenoids, alkaloids, etc. are found in *C. guianensis* flowers. The renal toxicity and lipid peroxidation caused by chloramphenicol were seen to decrease the antioxidant (GSH and CAT) which were ameliorated by the use of methanolic extract of *C. guianensis* flowers. Because the plant contains potent phytocompounds, the methanol extraction of the *C. guianensis* flower decreased the elevated levels of blood urea nitrogen and LPx (Landge, 2021). Isatin that can prevent dopamine depletion was extracted from the cannonball tree's flower parts, and it showed cytotoxicity and antioxidant properties against HL60 cells (Premanathan *et al*., 2012). It is anticipated that the antioxidant potential of the flower extract is mainly due to its phenolic components.

7.4 Anti-inflammatory activities of *C. guianensis* flower

The *C. guianensis* plant's ethanol extract has anti-inflammatory properties, partially because of decreased cell migration and decreased production of cytokines and inflammatory mediators (Pinheiro *et al*., 2013). Heat-induced HRBC membrane stabilization assay of methanolic extract of *C. guianensis* flower showed promising *in vitro* anti-inflammatory activity. An *in vitro* anti-inflammatory study in HRBC showed that at 500 mg/ml, the methanolic extract has strong anti-inflammatory action, that is comparable to the extract of *C. guianensis* EF(67.90 ± 5.8) and standard medication (66.88 ± 4.3) (Sumathi and Anuradha, 2016).

7.5 Antibacterial activities of *C. guianensis* flower

Dichloromethane, chloroform, and ethyl acetate extracts of *C. guianensis* flower were investigated for their antibacterial efficacy against *Salmonella typhi, S. aureus, E. coli, Streptococcus pyogenes, and Klebsiella pnemoniae* being significant human pathogenic bacteria. Here, a 100 µl concentration of each extract showed a promising antibacterial effect (Premalatha and Ramar, 2019). Zones of inhibition against all six bacteria (*E. coli, S. typhimurium*, *P. mirabilis, P. aeruginosa, A. baumannii*, and *K. pneumonia*) were observed in the methanolic extract of the *C. guianensis* flower petals and anther, and they ranged in size from 12 to 18 mm (Akther *et al*., 2017). A greater inhibition of bacterial growth was seen in green AgNPs as compared to plant extract and $AgNO_3$ application alone (Singh *et al*., 2021, Babu *et al*., 2022). Gram-positive bacterial species are strongly inhibited by AgNPs extracted from *C. guianensis* flower petals. A maximal inhibitory zone of 16 mm has been found for *Bacillus subtilis*. The floral extract's potent antibacterial properties against many bacterial species can be attributed to a multitude of antibacterial chemicals such as flavonoids, phenols, compounds, isatin, and indiglumin (Logambal *et al*., 2023). Likewise, synthesized CuNPs also show good antibacterial activity against *Bacillus subtilis* as compared to *E. coli* (Logambal *et al*., 2022).

7.6 Antifungal activity of *C. guianensis* flower

C. guianensis flower extract exhibited better inhibitory activity against *C. albicans* at 100 mg/ml. Thus, the ethyl acetate extract of *C. guianensis* flower has the most favorable anti yeast effect against *C. albicans* showing MFC and MIC values of 25.0 and 12.5 mg/ml, respectively (Gothai *et al*., 2018).

7.7 Antidiabetic activities of *C. guianensis* flower

A 50% ethanol extract of *C. guianensis* dramatically lowered blood sugar levels in the post-prandial state. On the fourteenth day, when glucose and *C. guianensis* extract were administered, the PPBS after 120 min were lowered to be within reference range in comparison with the control group administered only with water. The extract stopped the hyperglycemia (Hassan *et al*., 2018). Supplementing *C. guianensis* flower aqueous and methanolic extracts (100 mg/kg) effectively lowered blood glucose levels in diabetic rats produced by alloxan showing their antidiabetic effects. Also, oral administration of both extracts (100 mg/kg body weight) plus metformin (100 mg/kg body weight) every day resulted in considerable improvements in diabetic mice (Morankar *et al*., 2013).

7.8 Antitumor activities of *C. guianensis* flower

The *C. guianensis* flowers consist of compound isatin and its derivatives which are cytotoxic to human cancer cell lines. Isatin

caused DNA fragmentation to initiate the apoptosis process. One of the biochemical indicators of apoptosis is DNA fragmentation produced by cleavage at the internucleosomal linker regions (Swapnalatha and Rajeswari, 2014). Flow cytometry was used to validate the isatin-induced apoptosis to clarify the degree and underlying reasons for apoptosis. Isatin extracted from the *C. guianensis* flowers showed cytotoxicity and antioxidant properties against HL60 cells (Premanathan *et al*., 2012). Isatin is a compound with an EC_{50} value of 72.80 µg/ml exhibiting dose-dependent toxicity against human promylocytic cancer of the blood HL60 cells. The FACS analysis confirms caspase-mediated cell death in tumors (Sundararajan and Koduru, 2014).

C. guianensis exhibited both *in vitro* anticancer efficacy and cellular toxicity toward Human promyelocytic leukemia (HL60) cells in comparison to normal cell lines. Research was conducted on the anticancer effects of *C. guianensis* extracted using chloroform and DMSO. HL60 cell lines were cultured with varying concentrations of DMSO *C. guianensis* extract growing in DMEM. The MTT assay was the most effective method for determining the viability of the cell, and the optical absorbance at 570 and 620 nm was used as a reference. At 10 mg/ml of extract concentration, the floral extract inhibited 50% proliferation (IC_{50}) of HL60 cell lines (Bindhu *et al*., 2021).

MCF-7 cell lines were treated with *C. guianensis* flower extracts. Both the ethanolic extract (ECG) and the ethyl acetate extract (EACG) demonstrated cytotoxic action when examined *in vitro*. When compared to conventional tamoxifen, which has less cytotoxic action, the above results showed that both the ethanolic and ethyl acetate extracts of *C. guianensis* flowers had *in vitro* cytotoxic activity against MCF-7 cell lines. The cytotoxic characteristics noted might be caused by the extracts' abundance of phenolic chemical components. Previous research revealed that components of phenolic compounds and flavonoids have antitumor action (Bhagyasri *et al*., 2014).

Ag NPs produced from *C. guianensis* flower extract demonstrated high anticancer activity in an *in vitro* cytotoxicity investigation against MCF-7, L929, and normal (fibroblast) cell lines, with varying cell ranges (Babu *et al*., 2022). AgNPs coated with extract constituents may have promoted apoptosis-induced cell death, which in turn reduced cell viability (Palai, 2022).

The newly developed gold nanoparticles from blossoms of *C. guianensis* were evaluated using FTIR, XRD, SEM, TEM, and UV-Vis spectroscopy. The anticancer potential of freshly generated gold nanoparticles has been found through comprehensive screening conducted utilizing DNA fragmentation, MTT assay, DAPI staining for apoptosis, and comet assay for DNA damage. Using the MTT assay, cell viability was determined over 120 h. AuNPs produced from *C. guianensis* flower extracts significantly damaged HL-60 cells in a concentration-dependent manner, with an IC_{50} value of 5.14 Mm (Geetha *et al*., 2013).

To investigate their potential as treatments for these diseases, phytochemicals from Cannonball, such as quercetin, o-coumaric acid, p-coumaric acid, and stigmasterol, were docked using SwissDock with signaling molecules and proteins linked to the cancer pathway, such as breast cancer type 1 (BRCA1) susceptibility protein (3PXD). While stigmasterol has demonstrated a higher affinity for most of these proteins, quercetin, p-coumaric acid, and o-coumaric acid have also demonstrated a reasonable level of binding with the proteins at their catalytic regions, making them potential therapeutic options (Chauhan *et al*., 2022).

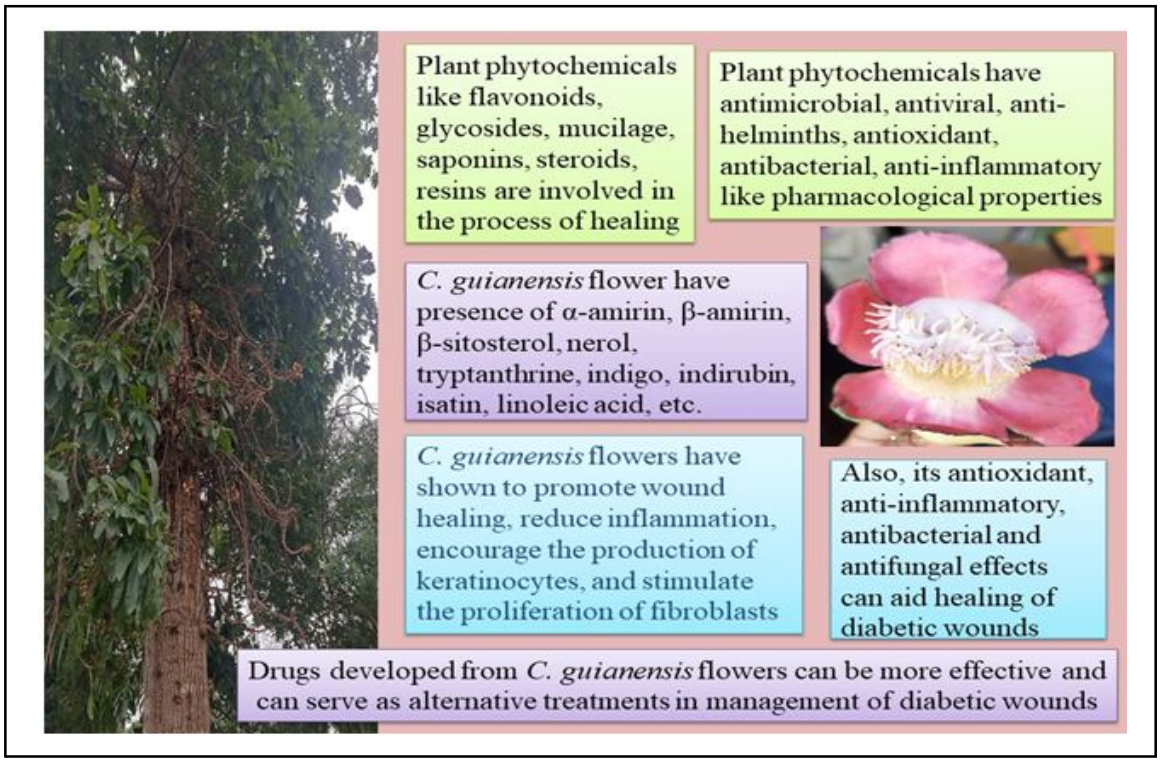

Figure 4: *C. guianensis* flowers can serve as alternative treatments in the management of diabetic wounds.

7.9 Hypocholesterolemic effects of *C. guianensis* flowers

The *C. guianensis* flower-supplemented group of Wistar rats had considerably lower ($p \leq 0.05$) values of triglycerides and total cholesterol than the control group. The polyphenolics and flavonoids in the *C. guianensis* flower can be the cause of the hypocholesterolemic effects which favorably altered the lipid profile (Niyas *et al*., 2021). The methanolic extract of *C. guianensis* flowers significantly reduced the levels of triglycerides, low-density lipoproteins, very low-density lipoproteins, and total serum cholesterol in obese rats while increasing high-density lipoproteins and the effect like that of standard Atorvastatin (Ramyasai *et al*., 2013).

7.10 Immunomodulatory effects of *C. guianensis* flower

The investigation of the flowers of *C. guianensis* showed significant immunomodulatory effects. PMNs exhibited a considerable increase in phagocytic activity *in vitro* upon exposure to the SME. SME efficiently enhances the non-specific immune response, as demonstrated by an enhanced phagocytic index and a larger percentage of PMN cells engaging in phagocytosis when compared to controls (Rege and Dahanukar, 1993).

Increased hypersensitivity responses to SRBCs were seen *in vivo* following SME treatment, which may indicate improved cellular immunity. At dosages of 100 and 200 mg/kg, the extract significantly influenced both early and delayed hypersensitivity reactions. This implies that SME increases leukocyte migration and activation, which strengthens the body's cellular immunological functions (Doherty, 1981). Moreover, increased antibody titers against SRBCs demonstrated that SME enhanced the humoral immune response. This suggests that the extract contributes to a stronger humoral immune response by increasing the generation of antibodies and promoting lymphocyte activity (Mediratta *et al*., 2002).

7.11 Genotoxicity and cytotoxicity of *C. guianensis* flower

The lethality assay on brine shrimp, used to track the bioactivity of the *C. guianensis* floral extract demonstrated that the *C. guianensis* flower extract is non-toxic to these shrimps. The extract showed extremely low toxicity, with an LC_{50} value of 1210.65 µg/ml (Gothai *et al*., 2019). When mice were given *C. guianensis* flower methanolic extract @ 2000 mg/kg (p.o.) dose, no death was observed even after seven days. The mice's normal clinical symptoms and lack of behavioral alterations strongly suggest that this floral extract has no harmful effects (Gupta *et al*., 2012).

8. Conclusion

Diabetic wounds are currently treated with a management protocol that includes skin substitutes, cytokine stimulators, cytokine inhibitors, MMPs inhibitors, bFGF, PDGF, VEGF, EGF, IGF-I, TGF-β, gene and stem cell therapies, ECM, and angiogenesis stimulators. These treatment plans for diabetic foot conditions are costly and have unfavorable side effects. Alternative therapy for treating diabetic wounds may include green manufacture of nano-formulations using medicinal plant parts. *C. guianensis* flowers that have been shown to promote wound healing, reduce inflammation, encourage the production of keratinocytes, and stimulate the proliferation of fibroblasts. Additionally, it has antioxidant, anti-inflammatory, antibacterial, and antifungal effects which will help promote healing of diabetic wounds. It also possesses antitumor, hypocholesterolemic, and antidiabetic effects with very less genotoxicities. These plant-based treatments might lessen the need for amputations after the aggravation of diabetic wounds. Drugs developed from *C. guianensis* flowers can be more effective as well as cost-effective alternative treatments in controlling and managing diabetic wounds. However, more studies are necessary to properly establish the significance of *C. guianensis* flowers in diabetic wounds.

Abbreviations

AAEq: Ascorbic acid equivalent

AGEs: Advanced glycation end-products

$AgNO_3$: Silver nitrate

AgNPs: Silver nanoparticle

AuNPs: Gold nanoparticles

bFGF: Basic fibroblast growth factor

CAT: Catalase

CuNPs: Copper nanoparticles

DAG: Diacylglycerol

DM: Diabetes mellitus

DMEM: Dulbecco's Modified Eagle's Medium

DMSO: Dimethyl sulphoxide

DPPH: 2,2-diphenyl-1-picrylhydrazyl

EC_{50}: Half maximum effective concentration

ECM: Extracellular matrix

ECM: Extracellular matrix

EDHF: Endothelium-derived hyperpolarizing factor

EF: Ethanolic fraction

EGF: Epidermal growth factor

FACS: Fluorescence-activated cell sorting

FDA: Food and Drug Administration

FTIR: Fourier Transform Infrared Spectroscopy

GPx: Glutathione peroxidase

GSH: Glutathione

GST: Glutathione s-transferase

HL60: Human promyelocytic leukemia 60

HRBC: Human red blood cell

IC_{50}: Half-maximal inhibitory concentration

IGF-I: Insulin-like growth factor I

IL: Interleukin

LC_{50}: Lethal concentration 50%

LPx: Lipoprotein X

MCF: Michigan Cancer Foundation-7

MeOH: Methanol

MFC: Minimum fungicidal concentration

MIC: Minimum inhibitory concentration

MMPs: Matrix metalloproteinases

MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

NADPH: Nicotinamide adenine dinucleotide phosphate

NO: Nitric oxide

PDGF: Platelet-derived growth factor

PDGF-BB: Platelet-derived growth factor

PKC: Protein kinase C

ROS: Reactive oxygen species

PMNs: Polymorphonuclear leukocytes

SEM: Scanning electron microscopy

SME: Successive methanolic extract

SOD: Superoxide dismutase

SRBCs: Sheep red blood cells

TEM: Transmission electron microscopy

TGF-β: Transforming growth factor beta

TIMPs: Tissue inhibitors of metalloproteinases

TNF-α: Tumor necrosis factor-alpha

VEGF: Vascular endothelial growth factor

XRD: X-ray Diffraction

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Santwana Palai, Sk Abdul Rashid, Ritun Patra, Sarita Jena, Biswakanth Kar, Sabitri Bindhani and Kautuk Kumar Sardar (2024). Biological activities and diabetic wound healing potential of *Couroupita guianensis* Aubl. flowers: Current knowledge and concepts. Ann. Phytomed., 13(2):44-54. http://dx.doi.org/10.54085/ap.2024.13.2.5.**