IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138
INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG
An International Open Access, Peer-reviewed, Refereed Journal

AN OVERVIEW OF *COMBRETUM INDICUM* L. AND ITS POSSIBLE PHARMACOLOGICAL IMPLICATIONS

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Abstract: *Combretum indicum*, a member of the combretaceae family, is commonly known as Rangoon creeper or Madhu Malti. It is a medicinal plant with a rich traditional history in various cultures. Different parts of *Combretum indicum* contain a variety of secondary metabolites as quisqualic acid, myristic acid, arachidonic acid, flavonoids glycoside, alkaloids, rutin, tannins, palmitic acid, kaempferol and two forms of the cysteine synthase, isoenzyme A and isoenzyme B with diverse pharmacological activities. These substances contribute to the plant's potential medicinal properties, such as antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Moreover, its constituents also show therapeutic implications in the diabetes, bacterial and helminthic infections. The present review emphasizes the possible pharmacological implications of extracts and secondary metabolites derived from *Combretum indicum* and its importance as a valuable natural resource. Furthermore, highlighted in this review are the pathways and mechanisms via which the *Combretum indicum*'s compounds produce their effects.

Keywords: *Combretum indicum*, Madhu Malti, Rutin, Flavonoids, Therapeutic Implications, Rangoon Creeper etc.

I. INTRODUCTION

Combretum indicum is an ornamental, fast growing, beautiful, fragrant, perennial vine. It is the member of combretaceae family. *Combretum indicum* thrives in warm climates and prefers well-draining soil and ample sunlight[5,12,19]. It prized for its clusters of sweet smelling, tubular blossom that change colour as they mature, starting as white, turning pink, and finally deepening into a crimson red[9]. It holds significance in traditional herbal medicine practices, where extracts from its various parts are utilized for their medicinal properties[1]. *Combretum indicum*, with its captivating flowers, versatility, and cultural significance, continues to enchant enthusiasts, making it a cherished addition to gardens[11] and landscapes worldwide[13].The plant, often referred to as the Chinese honeysuckle[27], or Quisqualis-indica L, goes by various names in different languages, each distinctive and unique to its cultural significance.

II. TAXONOMICAL CLASSIFICATION[13,16,17,19,28]:

Kingdom: Plantae
Phylum: Angiosperm
Division: Magnoliophyta
Class: Magnoliopsida
Order: Myrtales
Family: Combretaceae
Genus: Combretum
Species: C. indicum
Binomial Name: *Combretum indicum* (L.)
Synonym: Quisqualis indica L

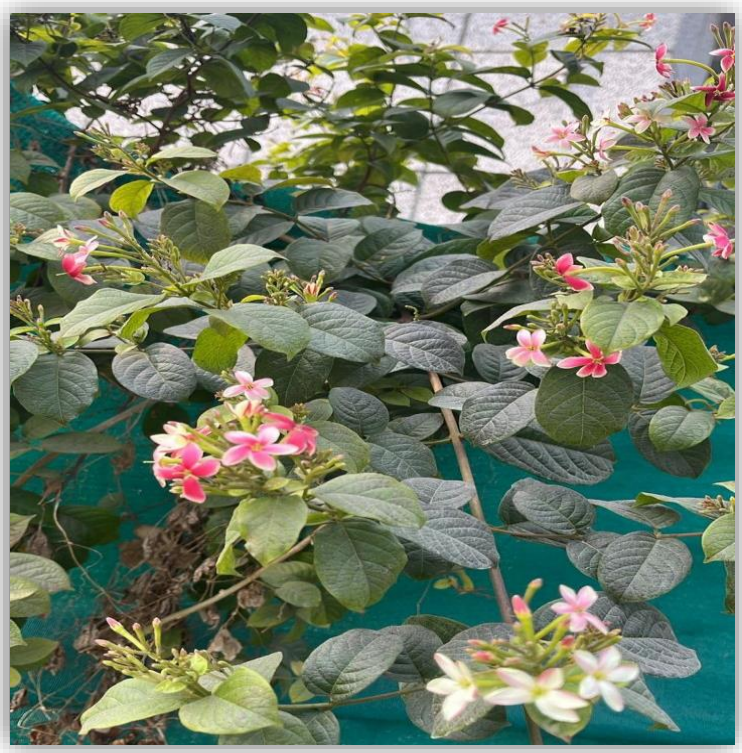

Figure 1: Leaves of *Combretum indicum*

III. VERNACULAR NAMES (REGIONAL NAMES):

English: Rangoon creeper[14,23]
Hindi: Madhu Malti, मधु मालती
Bengali: Madhabilata, Basantilata[14,23]
Tamil: Irangunmalli
Telugu: Mutyasaramu, Radha-Mahoharam[16,19]
Marathi: Rangoonvel, Madhumalti, Vilayati-Chambeli[16,23]
Gujarati: Madhura mallige, Barmasi vel
Malayalam: Ananthamballi
Spanish: Quiebra cercos
Assamese: Togorloti
Kannada: Madhura mallige
Manipuri: Parijat[19]
Malay: Akar dani[19]
Sanskrit: Madhusrava, मधुस्रवा
China: Shih-Chun-Tzu[28]

IV. ORIGIN AND GEOGRAPHICAL DISTRIBUTION:

The plant is widely cultivated in tropical[11] and subtropical regions around the world for its ornamental value[5,16]. It is more commonly seen and cultivated in regions closer to sea level or in areas with lower altitude ranges, where the climate is warm and humid, which best suits its growth and flowering. Its growth thrives in consistently warm temperatures, ideally ranging from 20°C to 35°C (68°F to 95°F). It is sensitive to frost and lower temperatures. Freezing temperatures can damage or kill the plant *Combretum indicum* grows well in a slightly acidic to neutral soil pH range, typically between 6.0 to 7.5.

The exact origin of *Combretum indicum* is traced back to its native regions, primarily in countries like India, Myanmar (formerly Burma), and Malaysia. *Combretum indicum*'s origins in India and Myanmar mark its natural habitat, but its widespread cultivation and adaptability have led to its presence in many tropical and subtropical areas worldwide. *Combretum indicum* is cultivated in various countries around the world[23], primarily for ornamental purposes[13,27] due to its attractive flowers and vine-like growth.[16] Some of the countries where it's cultivated include[11] the United States, Australia, Brazil, South Africa, the Philippines[23], Caribbean islands, India, and various Southeast Asian nations. *Combretum indicum* is also cultivated in Thailand, Malaysia, Indonesia, and Myanmar for its ornamental value.[23] *Combretum indicum*, is found in multiple states across India. Here are several states where you can find this plant: Kerala, Karnataka, Maharashtra, West Bengal, Tamil Nadu, Andhra Pradesh and Telangana, Uttar Pradesh, Assam, Rajasthan. These states cover a range of climates suitable for the growth of Combretum indicum, making it a fairly widespread plant across different regions of India.

V. PLANT MORPHOLOGY:

Combretum indicum is a woody, evergreen[16] or semi-evergreen climbing shrub. It exhibits a vine-like growth habit, often climbing over structures or other plants for support. It can reach heights of up to 8 meters (26 feet)[13,19,26] or more, showcasing its climbing ability. Its vine-like growth and ability to cover surfaces make it a popular choice for decorative purposes in landscaping.

Leaves: Leaves are simple, opposite or sub-opposite, meaning they grow in pairs along the stem, positioned across from each other or slightly staggered. The shape of the leaves is elliptic to ovate[17], with a pointed or rounded tip and a tapering base. They have entire margins (smooth edges). Typically, the leaves are 5-10 cm (2-4 inches) long and 2.5-5 cm (1-2 inches) wide leaves are smooth, glossy, and dark green in colour on the upper surface, while the underside may be lighter in shade.

Flowers: Flowers are arranged in terminal panicles (loose, branching clusters). The tubular flowers are fragrant and undergo a colour change as they age. They start as white, gradually turning pink, and finally deep red as they mature.[5] Each flower is about 2-3 cm long and consists of a slender tube with five spreading lobes at the end. This plant's ability to display multiple shades of flowers simultaneously along its vines makes it an eye-catching addition to any garden, trellis, or arbor.

Fruits: Fruit of this plant produces small, round, four-winged capsules containing numerous small, brown seeds. These capsules are about 1-1.5 cm in diameter.

Stems: Stems are woody, often with tendrils aiding in climbing, and can be reddish-brown or greenish-brown in colour. Upon reaching maturity, the fruit exudes an almond-like flavour on the palate.[16]

VI. THERAPEUTIC USES:

The therapeutic virtues of *Combretum indicum* Linn. have been well-documented in various traditional medicinal systems such as Ayurveda, Siddha, Unani, and others. Virtually every part of the plant is harnessed either independently or in combination with other substances to formulate remedies for diverse ailments.[2] For many years, the traditional uses of *Combretum indicum* have involved utilizing various parts of the plant, including flowers, leaves, and bark.[7] In Indonesian cuisine, the inclusion of these flowers in salads serves to infuse a burst of colour and elevate the visual allure of the dish. Flowers of *Combretum indicum* are used in the traditional dyeing of silk textiles.[13] This plant is traditionally used for cell aging or other oxidative stress-related diseases.[9]

VII. USES OF COMBRETUM INDICUM IN AYURVEDA:

Combretum indicum, known as "Madhumalati" in Ayurveda, has several traditional uses within this ancient system of medicine such as- anti-inflammatory, antioxidant benefits, digestive aids, fever-reducing, and skin-beneficial properties. Additionally, it is used to support respiratory health, manage diabetes, and as an adaptogen to help the body adapt to stress. Its traditional uses aim to address various health concerns, reflecting its versatile role in Ayurvedic formulations.[15]

VIII. CHEMICAL CONSTITUENTS:

Combretum indicum is known to contain a variety of compounds, including alkaloids, carbohydrates, flavonoids, tannins, terpenoids, glycosides, saponins, and phenolic compounds[18]. Quisqualic acid, myristic acid, arachidonic acid, flavonoids glycoside, alkaloids, pelargonidin 3- glucoside, rutin, tannins, palmitic acid, diphenylpropanoids, stearic acid, kaempferol, 1,2,4-oxadiazolidin-3, oleic-acid, 5-dione derivative, methylursolate, α-xylofuranosyluracil, triterpenoids, arjunolic acid, dihydrocucurbitacin linoleic acid[14,16] and two forms of the cysteine synthase, isoenzyme A and isoenzyme B (enzyme).[16] These substances contribute to the plant's potential medicinal properties, such as antioxidant, anti-bacterial, anti-cancer, antipyretic activity, immunomodulatory activity, anthelmintic activity, and antiseptic activity etc.[14]

Leaves: Leaves are rich in Trigonelline, L-proline, L-asparagine, quisqualic acid, rutin and two forms of the cysteine synthase, isoenzyme A and isoenzyme B. Nguyen Thi Hoai Thu *et al*. isolated three triterpenes, asiatic acid (**1**), arjunolic acid (**2**), and oleanolic acid (**3**), four aromatic compounds, benzyl-β-D-xylopyranosyl-(1″ → 6′)-β-D-glucopyranoside (**4**), nudifloric acid (**5**), vanillin (**6**), and gallic acid (**7**), and a sterol, *β*-sitosterol (**8**) from the leaves of *Combretum* indicum.[36]

Flowers: Sahu J, Patel *et al*. isolated rutin, pelargonidin-3-glucoside, and polyphenol from the flowers of *Combretum* indicum.[28]

Fruits: An organic acid that resembles cathartic acid and a sugary substance that resembles levulose are found in fruits of *Combretum* indicum[28]

Seeds: The Seeds of *Combretum indicum* are rich in a fixed oil comprising linoleic, oleic, palmitic, stearic, and arachidic acids, along with a sterol, an alkaloid possessing anthelmintic properties, and the neuroexcitatory amino acid quisqualic acid.[28]

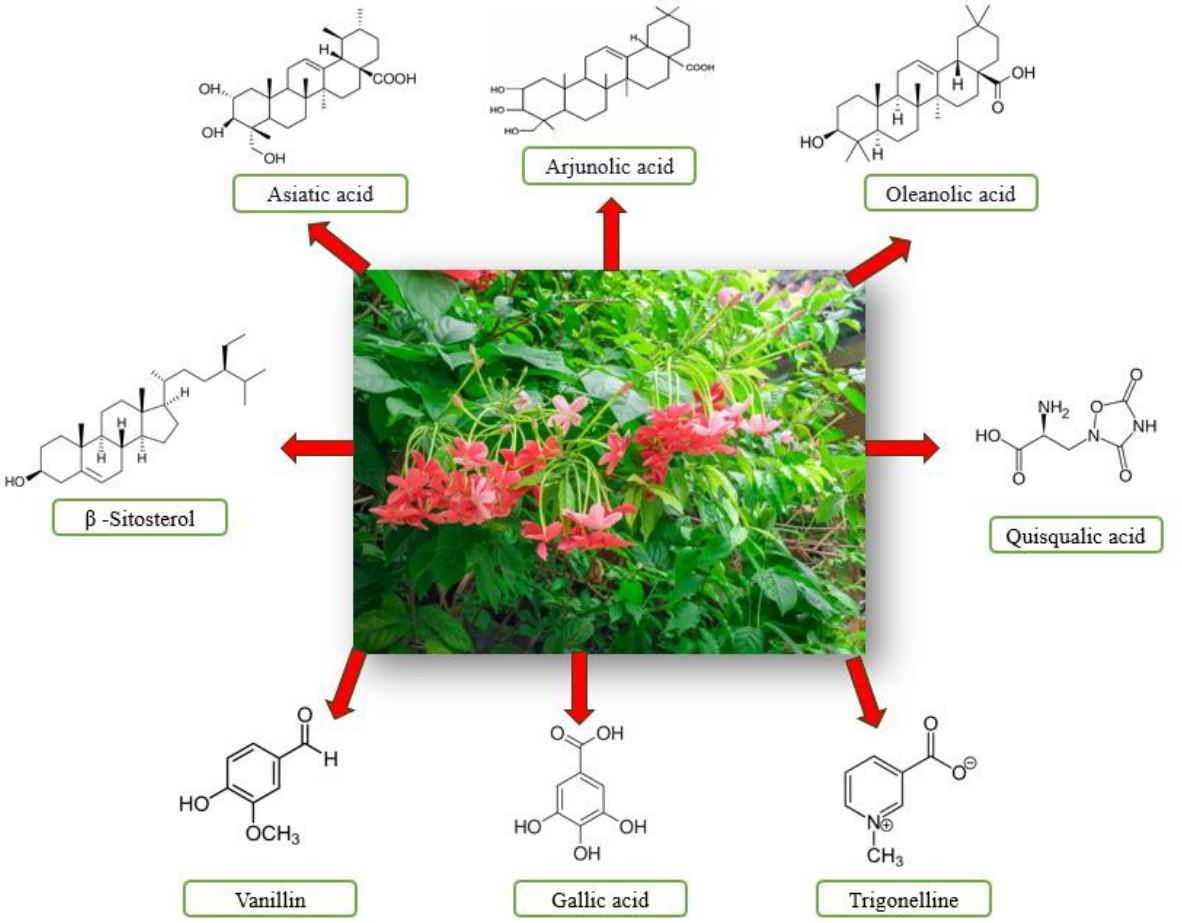

Figure 2: Chemical Structure of Major Constituents of Leaves of *Combretum indicum*

Table 1: Important Phytoconstituents of *Combretum indicum*

S. No.	Plant Parts	Phytoconstituents	References
1	**Leaves**	Trigonelline, L-proline, L-asparagine, arjunolic acid, asiatic acid, oleanolic acid, benzyl-β-D-xylopyranosyl-(1″ → 6′)-β-D-glucopyranoside, nudifloric acid, vanillin, gallic acid, and a sterol, *β*-sitosterol.	**[34, 36]**
2	**Flowers**	Rutin, pelargonidin-3-glucoside and polyphenol	**[4, 34, 31]**
3	**Fruits**	Cathartic acid (Organic acid) and a sugary substance (like levulose)	**[28]**
4	**Seeds**	Linoleic, oleic, palmitic, stearic, and arachidic acids, sterol, quisqualic acid	**[28]**
5	**Stem**	Diphenylpropanoids, Kaempferol, arjunolic acid, dihydrocucurbitacin F	**[24]**
6	**Roots**	Alkaloids, polyphenols, fatty acids and carbohydrates.	**[25]**

IX. PHARMACOLOGICAL ACTIVITIES:

Different parts of *Combretum indicum* plants such as leaf, fruit, root, seed, and flowers show role in disease management through modulation of various biological activities

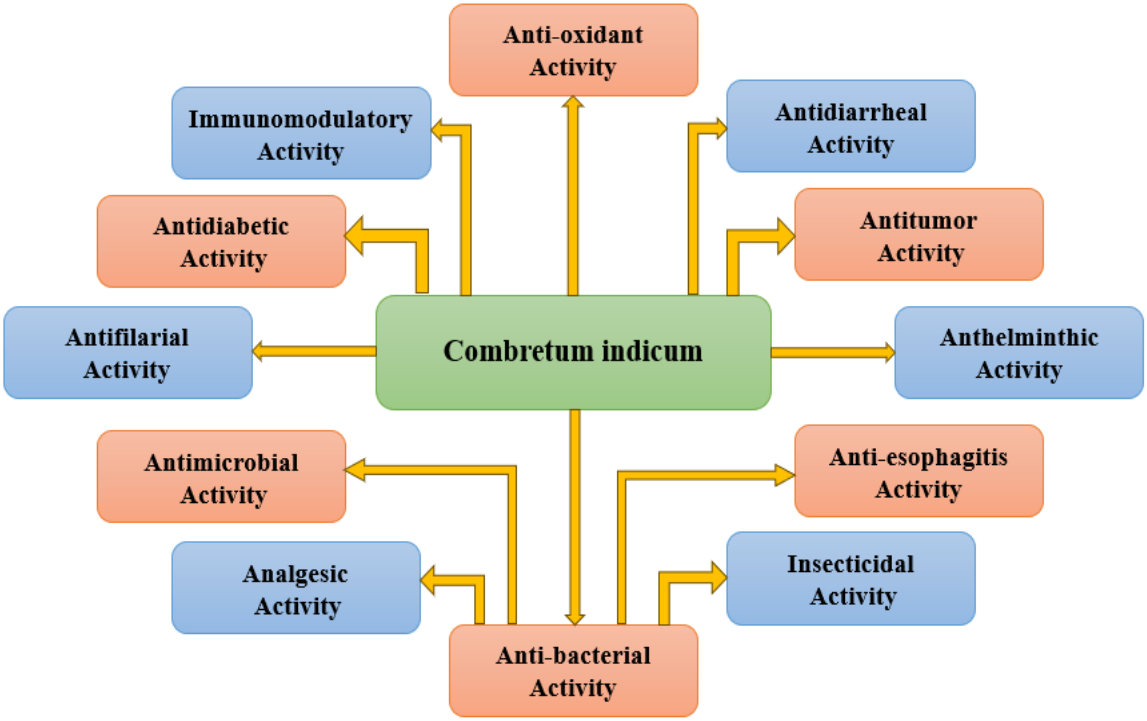

Figure 3: Pharmacological Activities of *Combretum indicum*

1. Anti-oxidant Activity: A study was performed by Hossain Md. Abu Hanif *et al* to evaluate the antioxidant activity of methanolic extract of leaves of *Combretum indicum*. Anti-oxidant activity was assessed by DPPH radical scavenging assay and reducing power capacity assay. Ascorbic acid (AA) was used as standard. The results suggest that extracts from leaf exhibits a dose-dependent scavenging of DPPH with IC50 48.87 µg/ml while in standard AA showed an IC50 value of 21.14 µg/ml which indicate its potent antioxidant activity. In reducing power capacity assay, the extract was put on view moderate action in a dose-dependent way.[14]

Mechanism of Action:

A number of researchers investigated that the presence of various polyphenolic compounds in the plants was the cause of their antioxidant actions. Polyphenolic compounds include flavonoids, tocopherols, tannins, and other organic acids. It has been well established that these compounds can exert synergistic effects on scavenging free radicals. Phenolic compounds have antioxidant activity by reacting with free radicals. Polyphenols function as antioxidants through two distinct pathways.[14]

1. Scavenging of free radicals (direct) by-
   a) The transfer of H-atom(s) from the OH group(s) of polyphenols to the free radicals.
   b) Transfer of single electrons to the free radicals.
   c) Chelation of transition metal ions, particularly Fe^{2+} and Cu^{2+}, to limit the formation of $HO^{\bullet}$.
2. Activation of the synthesis of ROS-removing enzymes by activation of Nrf2, which in turn translocates to the nucleus, attaches itself to the antioxidant response elements (AREs), and thus activates antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).[6]

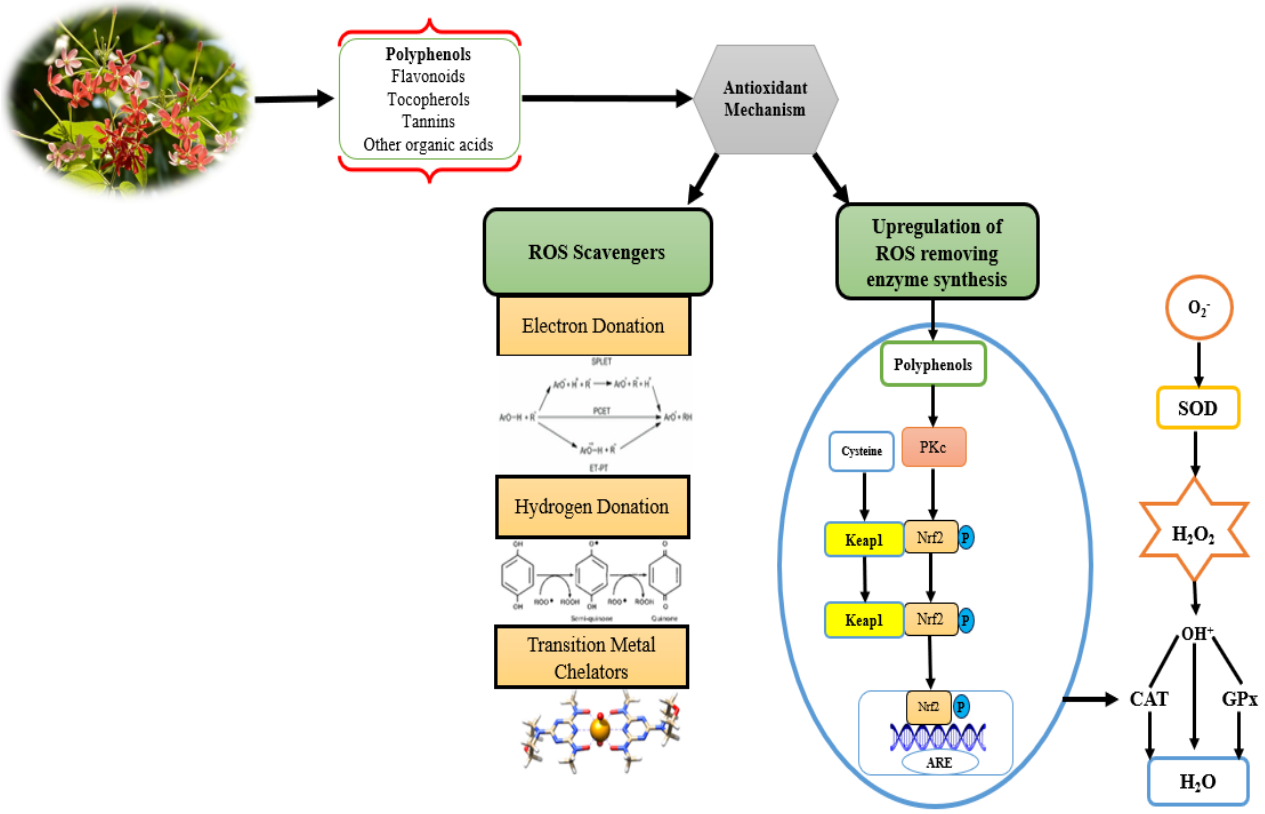

Figure 4: Antioxidant Effects of Polyphenols

2. Antibacterial Activity: Kumar Manoj *et al*. examined the antibacterial activity of *Combretum indicum* Linn. flower extracts in methanolic, ethanolic, and aqueous forms against strains of gram-positive and gram-negative bacteria, including Micrococcus luteus, Bacillus subtilis, and Escherichia coli. The antibacterial activity of the extracts was assessed using the Agar well diffusion test method. In comparison to the ethanolic and aqueous extracts, the methanolic extract of *Combretum indicum* had the greatest effectiveness and the broadest inhibitory zone.[3,20] Using three different solvents- methanol, ethyl acetate, and hexane Agarwal A *et al*. (2016) also found antibacterial activity in the dried aerial part of *Combretum indicum*. The broth dilution method was used to measure the antibacterial activity. When compared to ampicillin, which was used as a positive control, all extracts shown considerable action against the four pathogens *Escherichia coli*, *Klebsiella pnemoniae*, *Staphylococcus aureus*, and *Staphylococcus pneumonia*. The results revealed that the methanol extract exhibited the lowest Minimum Inhibitory Concentration (MIC) against *E. coli*, the hexane extract was most effective against *Klebsiella pneumoniae*, and the ethyl acetate extract showed the lowest MIC against *S. pneumoniae*. Interestingly, all three extracts demonstrated similar MIC values against *S. aureus*.[2]

Mechanism of Action: Numerous studies have examined the potent antibacterial activity of polyphenols and alkaloids. Among the most abundant and varied classes of secondary metabolites, polyphenols' antioxidant properties serve as the foundation for their antibacterial actions. Bacterial cell membranes are bound by polyphenols in a concentration-dependent way that modifies the membrane's functional properties and inhibits the growth of the bacteria.

3. Anthelminthic Activity: The medication *Combretum indicum* L., also known locally as Eeshwara hoovu, is used by the folkloric people of Dakshina Kannada, District, Karnataka, to cure helminthiasis. In order to scientifically verify the folklore about the drug *Combretum indicum* L., an experimental investigation was conducted using adult Indian earth worms (*Lumbricus terrestris* L.). Albendazole suspension was used as the standard drug for comparison The investigation demonstrated the superior experimental efficacy of *Combretum indicum* L. over the standard drug in the experimental setting.[17]

Mechanism of Action: An assessment was conducted on the anthelmintic activity of forty extracts derived from 10 plants that were utilised in Benin to treat small ruminant intestinal parasitosis. According to these findings, a number of substances, such as terpenes, flavonoids, alkaloids, and tannins, may be partially responsible for the biological activity that has been seen. Their mechanism of action is different. Tannins are polyphenolic substances that attach themselves to free proteins in worm guts. This can interfere with the worms' energy generation mechanism, causing paralysis and death. Moreover, tannins can strengthen the host's defences against intestinal parasites. Alkaloids can break down cell walls, proteins, and lipid content in worms, resulting in death. Flavonoids can cause proteins in the cuticle and intestine to clump together, which can paralyze the worm's muscles and eventually kill it.

4. Antifilarial activity: Rastogi S *et al*. reported in vitro antifilarial activity of ethanolic and hydroethanolic extracts of the leaves and flowers of *Combretum indicum* on microfilariae (mf) and female adult worms of human lymphatic filariid Brugia malayi. Antifilarial activity of the extracts was assessed using the motility and or 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT)-reduction assays. It was discovered that the hydroalcoholic extract of flowers was found effective as it killed adult female worms (LC100: 62.5 µg/mL) and mf (LC100: 125 µg/mL). SI values recorded with respect to motility of female parasite and mf was more than 20.[26]

5. Antitumor Activity: The methanolic extract derived from the aerial part of *Combretum indicum* exhibited notable anti-tumor activity when tested on *Ehrlich ascites* carcinoma cells. The entire extract demonstrated a significant impact on the viability of these carcinoma cells at all concentrations tested, displaying a dose-dependent response. Remarkably, the high concentration of the extract induced a cytotoxic effect comparable to that achieved by vincristine, a commonly utilized anticancer drug. The results

from the comprehensive examination of *Combretum indicum*'s aerial parts unequivocally suggest its potential as an antitumor agent, supporting its application in complementary therapeutic approaches.[1]

Mechanism of Action: Flavonoids can inhibit cell growth and act as an anticancer agent.

6. Anti-esophagitis Activity: The study reveals the efficacy of the alcoholic extract derived from *Combretum indicum* flowers in combating esophagitis through the inhibition of reactive oxygen species (ROS) and free radicals. This extract demonstrated the normalization of pH and total acidity in esophageal content, accompanied by an elevation in the levels of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). Moreover, there was a reduction in thiobarbituric acid reactive substances (TBARS) and protein carbonyl (PC) concentration. The results of the statistical analysis using SAM further supported the protective effects of *Combretum indicum* flower extract on esophageal tissue. These beneficial actions are likely attributed to the higher content of phenols and flavonoids present in the extract.[27]

7. In-vivo antidiabetic Activity: In a Long-Evans rat model, Md Shaekh Forid *et al*. examined the in vitro antioxidant and in vivo antidiabetic properties of *Combretum indicum* leaf extract (CILEx) using UPLC-QTOF/ESI-MS-based phytochemical profiling. The animals' lipid profiles, blood glucose levels, and pancreatic structures were assessed following a one-week intervention. The results indicated that CILEx has a very promising antioxidative impact. It was discovered that both CILEx doses increased high-density lipoprotein (HDL) and significantly ($p < 0.05$) decreased blood glucose, total cholesterol (TC), and low-density lipoprotein (LDL). When compared to the diabetic control group, the pancreatic tissue topologies were significantly better.[11]

8. Anti-microbial Activity: In the assessment of antimicrobial activity using the disk diffusion method, ethyl acetate extracts from various parts of *Combretum indicum* exhibited distinct profiles of bioactive compounds. Notably, the flower samples, both in their crude (102.24±0.48 mg GAE/g of tissue) and dry (83.75±0.47 mg GAE/g of tissue) forms, displayed the highest total polyphenolic content. Concurrently, the crude leaf extract (60.67±0.31 mg QE/g of tissue) and dry flower extract (54.27±0.20 mg QE/g of tissue) exhibited the highest total flavonoids content. Furthermore, when evaluating the antimicrobial efficacy, it was observed that the leaf extract displayed the maximum inhibitory zone against Staphylococcus aureus, while the flower extract exhibited the highest inhibitory zone against *Escherichia coli*. These findings underscore the differential bioactive substance distribution within the plant, emphasizing that the leaves and flowers of *Combretum indicum* contain high antimicrobial property compared to the stem.[9]

9. Immunomodulatory Activity: The hydroalcoholic extract of *Combretum indicum* flowers demonstrated proven immunomodulatory activity, as evidenced by the carbon clearance test, cyclophosphamide-induced myelosuppression, Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), and Delayed Type Hypersensitivity (DTH). Administered orally at 100 mg/kg and 150 mg/kg, the *Combretum indicum* flower extract exhibited significant immunomodulatory effects, with Levamisole (50 mg/kg, po) as the standard drug. Comparative analysis against the control group induced by cyclophosphamide (50 mg/kg) further confirmed the higher dose of *Combretum indicum* flower extract's notable immunomodulatory activity.[39]

10. Analgesic Activity: In wistar rats, Kavita Kumari *et al*. assessed the analgesic effect of a hydroalcoholic extract of *Combretum indicum* Linn. leaves. *Combretum indicum* leaf hydroalcoholic extract (100 and 200 mg/kg p.o.) was found to have peripheral analgesic action when tested on experimentally induced pain models, such as the tail flick method with analgesiometer and the acetic acid-induced writhing effect in albino wistar rats of both sexes. In every treatment group, the plant extracts demonstrated dose-dependent analgesic effect; the outcomes were contrasted with those of the conventional medication, aspirin (20 mg/kg, p.o.). The hydroalcoholic extracts of *Combretum indicum* Linn. leaves (100, 200 mg/kg, p.o.) demonstrated considerable analgesic effectiveness against pain generated in an experimental setting, with the effects decreasing with dosage.[21]

11. Antidiarrheal Activity: The petroleum ether extract of *Combretum indicum* L. leaves demonstrated significant dose-dependent anti-diarrhoeal activity in albino Wistar rats. Administered orally at doses of 100 and 200 mg/kg, the extract exhibited efficacy against experimentally induced diarrhoea models, including castor-oil induced diarrhoea and charcoal-induced gastrointestinal motility test. Comparative analysis with standard drugs (Loperamide and Atropine sulphate) further supported the conclusion that the petroleum ether extracts possess noteworthy anti-diarrhoeal effects at both doses ($P<0.05$).[30]

12. Insecticidal Activity: Ethanol extracts from thirty Chinese medicinal plants were tested for their insecticidal activity against Spodoptera exigua, as well as their contact toxicity and anti-feedant properties. Fruit from *Combretum indicum* was one of them. Eight Chinese medicinal plant preparations demonstrated potent insecticidal action. The plant extracts from Brucea javanica (L.) Merr., Artemisia argyi Lévl. et Vant., and Litsea cubeba (Lour.) Pers. proved to be the most efficacious. Strong antifeedant effects were seen in the insect by three of the extracts. Extracts from Bidens pilosa, Carpesium abrotanoides, Eclipta prostrasta, F. thunbergii, Lonicera japonica, Saposhnikovia divaricata, and *Combretum indicum* caused significant values of FDI (30 to 60%).[10]

X. CONCLUSION:

Natural product-based medications are becoming much more widely known, and there are many more advantages to using them. *Combretum indicum* is a versatile medicinal plant recognized for its traditional uses and therapeutic potential. *Combretum indicum* emerges as a promising candidate for further exploration in drug discovery and development due to its diverse phytochemistry and versatile pharmacological properties. This review provides valuable insights into the current state of knowledge regarding *Combretum indicum*, serving as a foundation for future research, including rigorous clinical trials, to validate and optimize the therapeutic potential of *Combretum indicum*. Additionally, the mechanism of action by which the constituents in *Combretum indicum* produce their effects are also discussed in this review. Through the modification of numerous cellular pathways, *Combretum indicum* and its constituents play a critical and crucial role in the treatment and prevention of disease in this context. This comprehensive review also lays the foundation for future investigations, emphasizing the importance of harnessing the medicinal properties of *Combretum indicum* for the development of effective and safe healthcare interventions. Further studies on its different types of ingredients are required to know the proper mechanism of action in health management.

XI. ACKNOWLEDGEMENT:

The authors are grateful to the Department of Pharmacology, Translam Institutes of Pharmaceutical Education and Research, Meerut for supporting this study.

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