Review Article

CHEMICAL CONSTITUENTS AND ANTI-INFLAMMATORY AND ANTI-OXIDANT AGENTS FROM COMBRETUM GENUS: A REVIEW

Abstract

Many diseases are treated using medicinal plants because they contain components that have therapeutic properties. The prevention and treatment of diseases linked to oxidative stress depend heavily on antioxidants.With over 20 genera and 600 species, the Combretaceae family is a vast group of plants, shrubs, and trees that is distributed tropically throughout the world, with centers of diversity in Africa and Asia. In traditional medicine, certain species of Combretum are widely used as diuretics and to treat bleeding, diarrhea, infections, diabetes, malaria, and inflammation. This work is a review of Combretum species that have been assessed for their biological activity. It is imperative that more research be done on Combretum species in order to generate novel therapeutic options that could potentially enhance the well-being of individuals with a range of ailments.

Keywords: Terpenoids, Flavonoids, Stilbens, Oxidative Stress, Inflammation

Introduction

Science has not yet fully tapped into the potential of most plants to generate new drugs, particularly in developing nations, despite their shown superiority in treating and managing a wide range of human and animal ailments. Medicinal plants are majorly used for therapeutic purposes or as precursors for the synthesis of useful drugs(Yahaya et al., 2021). As such there are two major classes of substance found in plants; the primary metabolites and the secondary metabolites also known as phytochemicals. However, through trial and error, humans have learned that under certain condition, physiological effects of some secondary metabolites can have therapeutic benefit(Sahreen et al., 2010). The medicinal effect from plants are as a result of the combination of secondary metabolites present in them. The primary metabolites like carbohydrates, protein, nucleic acids, chlorophyll and lipids plays more of nutritional role in plants and also help in the biogenesis of the secondary metabolites. For over a thousand years, medicinal plant plays a central role in the early stage of drug discovery by utilizing various bioassays to evaluate phytochemicals, in which the phytochemicals or its structural analogues could be putative drug candidate. It is on this note that we explore combretum genus belonging to combretaceace family in order to get insight on its therapeutic potentials.

OVERVIEW OF COMBRETUM GENUS

Combretum comprise of about 250 species and distributed throughout the tropics and subtropics. The species of *Combretum* are trees, shrubs, shrublets or woody climbers, very rarely sub herbaceous. Scales (subgenre. *Combretum*) or microscopic (sometimes macroscopic) stalked glands (subgenre. *Cacoucia*) are present. The subgenus *Combretum* is sometimes divided into eleven sections, based on the floral, scale and fruit anatomy (Jordaan et al., 2011; Kubitzki, 2007)

In the genus *Combretum* the leaves are opposite, verticillate or rarely alternate, usually petiolate, almost always with entire margins. The petiole is sometimes persistent, and especially in climbers it forms a hooked wooded spine when the leaf abscises. The flowers are hermaphroditic, regular or slightly zygomorphic, 4-5 merous and they are borne in elongated or sub capitate axillary or extra-axillary spikes or racemes or in terminal or terminal and axillary, often leafy panicles. The receptacle is usually clearly divided into a lower part (lower receptacle) surrounding and adnate to the ovary, and an upper receptacle which sometimes is differentiated into a lower part containing the disk and an often more expanded upper part. Sepals are 4-5 (rarely more), dentate to subjugate or filiform, sometimes scarcely developed. Petals are 4-5, small and inconspicuous or showy (white, purple, red) and exceeding the sepals.

Stamens are twice as many as the petals, inserted in 1 or 2 series inside the upper receptacle. The disk of the receptacle is glabrous or hairy, with or without a free margin, sometimes inconspicuous and absent. The fruit is 4-5 winged and ridged or angled, sessile or stipulate, indehiscent or rarely dehiscent; the pericarp is usually thin and papery, sometimes leathery, more rarely fleshy. Even if the fruits are often used as a good species identification character, species identification is not always easy at the fruiting stage (Van Wyk, 2013)

ETHNOBOTANICAL USE OF SOME *COMBRETUM* SPECIES

The genus *Combretum* are well known in African traditional medicine, and all parts of the *Combretum* species are used as medicine as shown in Table 1

Table 1 Ethnobotanical uses of some combretum species

Species	Plant part	Trado-medicine uses	Ref
C. molle	Roots, stem bark and leaves	Stomachache, wound healing, edema, skin diseases and gonorrhea	(Neuwinger, 2000) (Fyhrquist et al., 2002)
C. psidioides	Leaves and root	Diarrhea, muscle pain and edema	(Fyhrquist *et al.*, 2002)
C. padoides	Leaves and root	Bloody diarrhea, conjunctivitis, antimalarial, and wound healing	(Gathirwa et al., 2011; Nguta et al., 2010)

C. sericeum	Leaves, and root bark	Stomach disorder, wound, bone fracture and conjunctivitis,	(Codo Toafode et al., 2022; Sini et al., 2017)
C. fragrans	Leaves, root and shoots	Leprosy and diarrhea	(Ejidike et al., 2023)
C. woodii	Leaves	Abdominal pain, and venereal diseases	(Ahmed et al., 2014; Ejidike *et al.*, 2023)
C. zeyheri	Leaves and root	Scorpion and snake bites, mental problem, tuberculosis and pneumonia	(Roy et al., 2014)
C. collinum	Leaves	Earache, rheumatism, diarrhea, cough, and ascariasis	(Ejidike *et al.*, 2023; Marquardt et al., 2020)
C. paniculatum	Leaves and root	Enlarge spleen and liver, diarrhea, and dysentery	(Bekele et al., 2021)
C. leprosum	Leaves, flowers, stem and root barks	Wound healing, skin rashes, cough and heartburn	(de Oliveiraa et al., 2019)
C. erythrophyllum	Leaves, root and stem bark	Abdominal pain, leprosy, venereal diseases, and sores	(Mawoza et al., 2015)
C. apiculatum	Leaves	Stomach problems, scorpion stings, disinfect the navel after birth	(Silén et al., 2023)
C. micranthum	Leaves and roots	colds, fever, measles, bruises colic, vomiting, gastrointestinal problems and malaria	(Silén *et al.*, 2023; Suroowan et al., 2019)

C. imberbe	Leaves and root	Diarrhea, coughs, and toothpaste	(Ejidike *et al.*, 2023; Silén *et al.*, 2023)
C. kraussi	Leaves, root and stem bark	Body pain	(Ejidike *et al.*, 2023)

PHYTOCHEMISTRY OF SOME *COMBRETUM* SPECIES

The major compounds derived from the *Combretum genus* include but not limited to the flavonoids, terpenoids and stilbenoids.

TERPENOIDS

Terpenoids are the hydrocarbons of plant origin of the general formula $(C_5H_8)n$ as well as their oxygenated, hydrogenated and dehydrogenated derivatives. They are the most widespread, chemically interesting groups of secondary metabolites including steroids and have very wide range of biological acivities(Alamgir et al., 2018; Banik et al., 2022). The genus *Combretum* has yielded mainly pentacyclic triterpenoids varying from oleanoic acid(Dawe et al., 2013; Oluyemi et al., 2020).

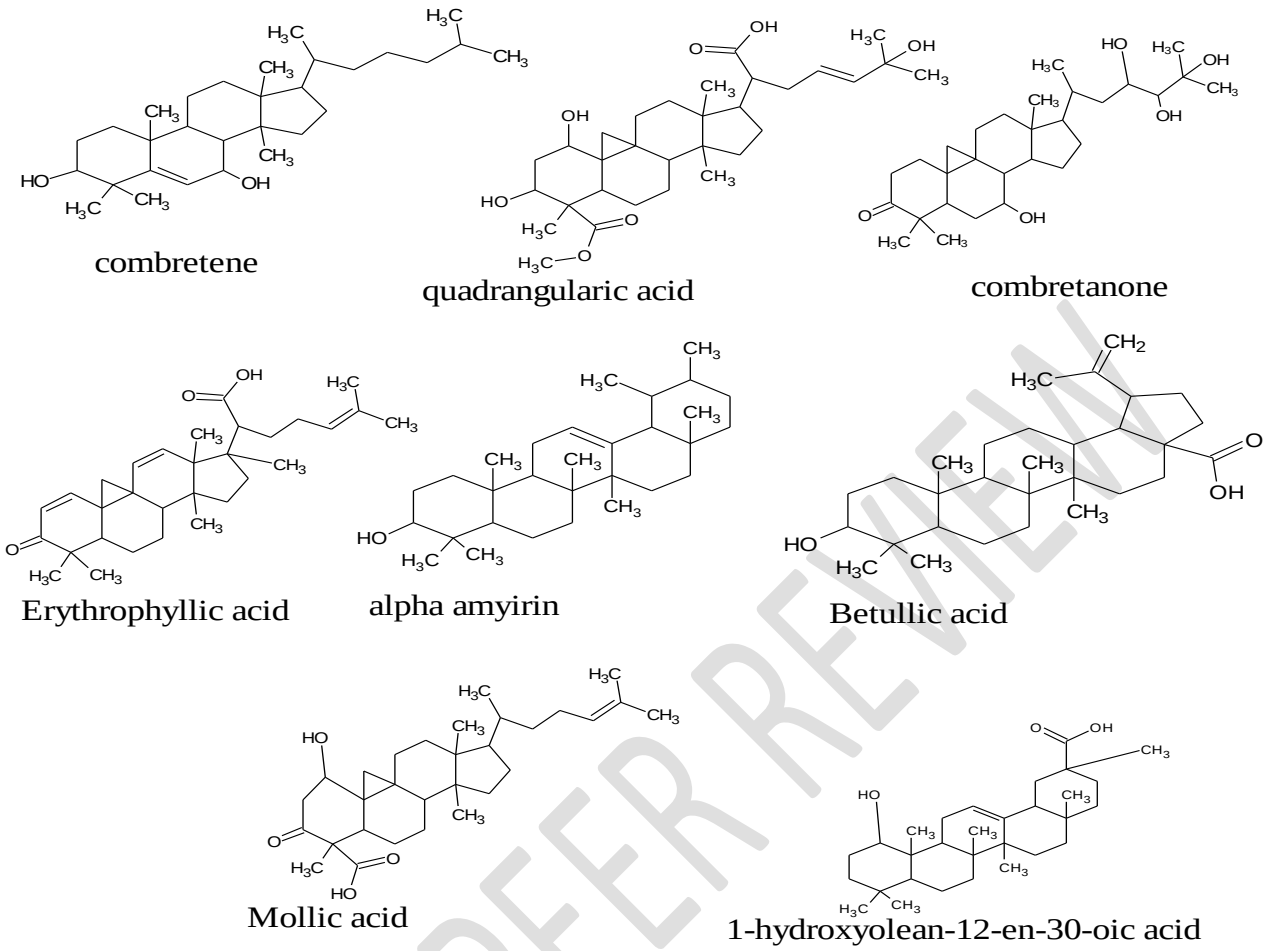

Fig 1: Sturcutres of terpenoids from some combretum species

FLAVONOIDS

Polyphenols are a widespread group of secondary metabolites found in all plants, representing the most desirable phytochemicals due to their potential to be used as additives in food industry, cosmetics, medicine and others fields.They are classified into various types depending on their chemical structure, degree of unsaturation, and oxidation of carbon ring. Anthoxanthins (flavanone and flavanol), flavanones, flavanonols, flavans, chalchones, anthocyanidins, and isoflavonoids are the different subgroups of flavonoids. Flavanones and flavones and chalcone types of flavonoids have been reported from *different parts of combretum species*(Katerere et al., 2012; Ngameni et al., 2013; Umoh et al., 2023).

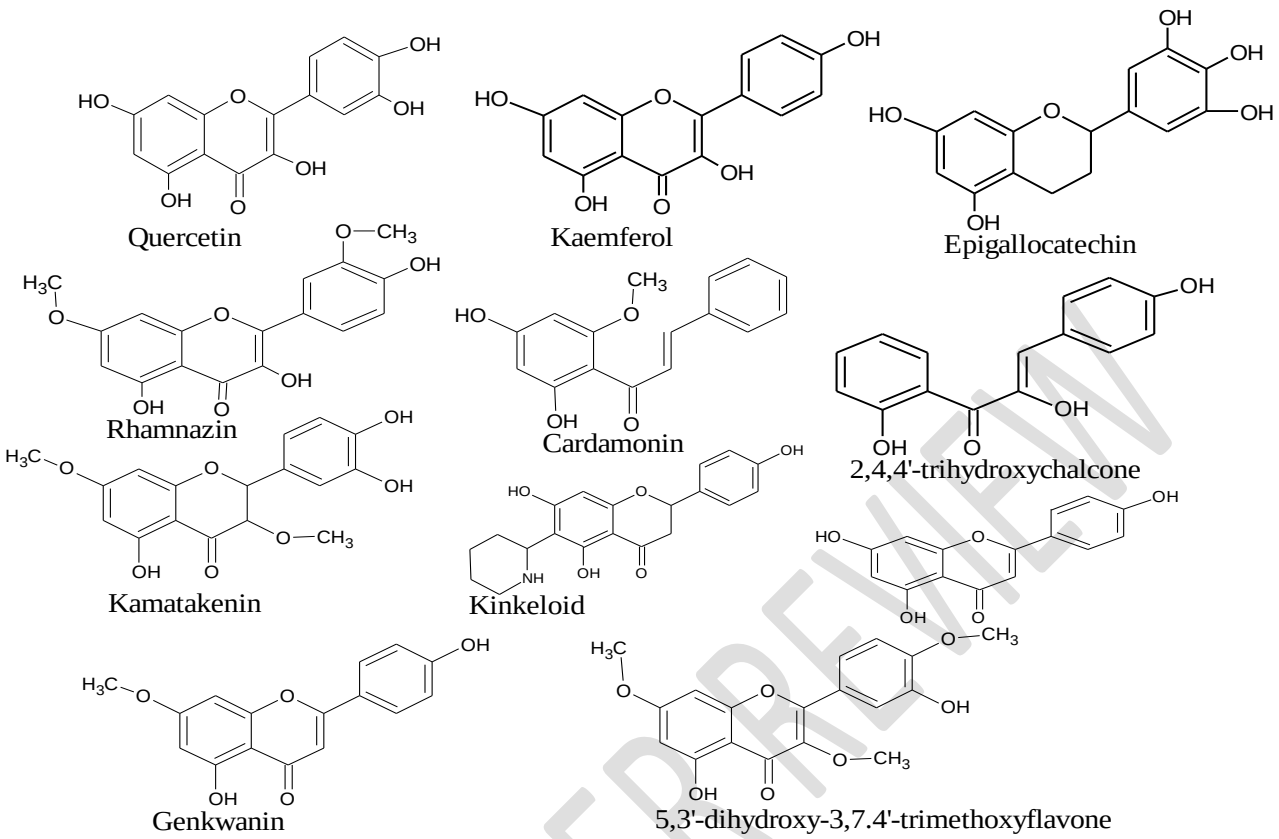

Figure 2: Structures of flavonoids isolated from some combretum species

STILBENES

Stilbenes are another class of compounds that are part of non-flavonoid polyphenols with 1,2-diphenylethylene as basic structure (Bento et al., 2017). They are non-flavonoids polyphenols compounds with three fused rings as basic structure. They are either precursors or products of the stilbene metabolic pathway and have been isolated from several *Combretum* species(Karatoprak et al., 2020; Teka et al., 2022; Tsopmo et al., 2013) including *C. erythrophyllum* , *C. molle* .

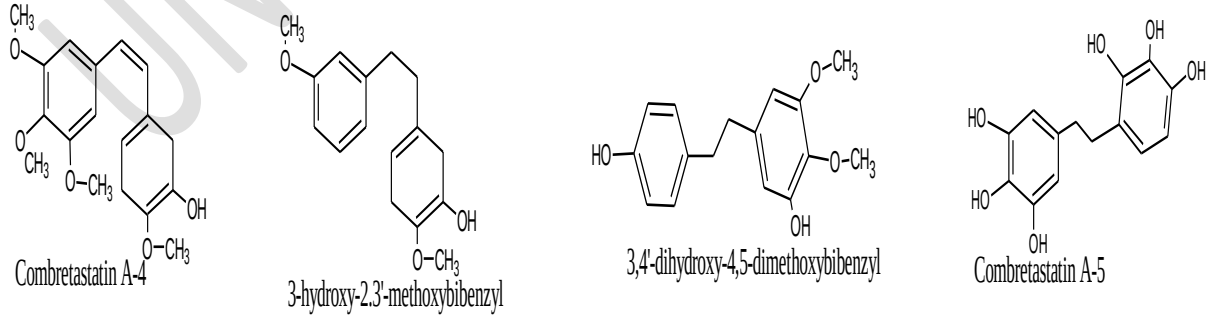

Figure 3: Structures of stilbenes isolated from combretum species

BIOLOGICAL ACTIVITIES OF SOME COMBRETUM SPECIES

Several scientific work have been reported on the potentials of combretum species in the treatment and management of various diseases condition of man. The records so far are encouraging as some active compounds with specific physiological effect on oxidative stress, hepatoprotection and inflammatory disorders have been identified**.**

OXIDATIVE STRESS

This arises due to inabilities of the body to neutralize reactive oxygen/nitrogen species (ROS and RNS) and eliminate them at the rate which they are generated in the system. The ROS are generated when cells are exposed to the environment with a lot of oxygen. ROS and RNS comprise of reactive unpaired electrons, (free radicals) hydroxyl radical and superoxide anion in addition to non-radical species that include hypochloric acid, singlet oxygen, hydrogen peroxide as well as ozone(Aranda-Rivera et al., 2022; V. Kumar, 2018). Antioxidantsare substances that stabilize free radicals to prevent their harmful effects on the tissues. They are also found in diet and may also safeguard the cells from the detrimental effects of free radicals, molecules that can damage cells. They terminate free oxygen species through enzyme-like superoxide dismutase (SOD), glutathione peroxidase (Gpx), and catalase and thioredoxin reductase. These molecules deter the process of oxidation by giving out an electron to a free radical making it neutral and harmless(S. Kumar et al., 2011; Moriasi et al., 2020). There are several antioxidants such as phenolic compounds that prevent free radicals from initiating a series of chemical reactions, also some have metal chelating capacity, Butylated hydroxytoluene (BHT), Butylated hydroxyl anisole (BHA). These are convectional antioxidants agent that reduce free radical production to amounts that are not harmful to the body. The conventional antioxidants are important but limited by their cost, failure rates and associated adverse effects such as low blood glucose, liver damage and carcinogenesis(Neha et al., 2019). With the shortcomings of conventional drugs in the management and treatment of oxidative-stress related disorders, the need to alternative therapy is vital. The use of plant-derived therapy is the best alternative because they are readily available, inexpensive with little or no side effect (Hano et al., 2020; Kim et al., 2023). This involves the use of products that are naturally available hence not very expensive compared to the synthetic antioxidants. Based on several studies medicinal plant has been shown to possess antioxidant potential which is attributed to high concentration of phenolic compounds present in the plants part(Singh et al., 2016). The antioxidant effect of some combretum species is presented in Table 2

Table 2: **Antioxidant activity of some combretum species**

Name of plant	Part of plant	Model	Remarks	Ref.
C. quadrangulare	Leaf	ABTS and DPPH	Significant activity	(Men et al., 2022; Yen et al., 2024)
C. latifolium	Leaf	ABTS and	Significant	(Nopsiri et al.,

		DPPH	activity	2014; Pilaquinga et al., 2021)
C. decondrum	Leaf	ABTS and DPPH	Significant activity	(Nopsiri *et al.*, 2014)
C. roxburghii	Leaf and stembark	DPPH	Significant activity	(Bhatnagar et al., 2012; Das et al., 2020)
C. albidum	Leaf	DPPH	Significant activity	(Das *et al.*, 2020; Parusnath et al., 2023)
C. quadrangulare	Fruits	ABTS, DPPH, RP and TAC	Significant activity	(Men *et al.*, 2022; Yen *et al.*, 2024)
C. hartmannianum	Leaf	ß-carotene–linoleic acid and DPPH	Significant activity	(Mariod et al., 2006)
C. acutum	Leaf	ABTS, FRAP and DPPH	Significant activity	(Coulidiati et al., 2011)
C. sericeum	Aerial part	ABTS, FRAP and DPPH	Significant activity	(Coulidiati *et al.*, 2011)
C. nioroense	Leaf	ABTS, FRAP	Significant activity	(Coulidiati et al., 2009)
C. molle	Leaf and Fruit	DPPH, NO and superoxide scavenging assays	Significant activity	(Rademan et al., 2019)
C. paniculatum	Leaf and root	DPPH	Significant activity	(BEKELE, 2018)

INFLAMMATION

Inflammation is a biological response of body tissues towards various harmful stimuli. It is known to be initiated as a normal body defense mechanism during injury, exposure to contaminants, radioactive substances, toxicants as well as allergens and infection by a plethora of agents like microbes, viruses. It is associated with the characteristics like pain, swelling, redness, loss of function in the affected area and

heat accumulation in the inflamed area(Ayertey et al., 2021). Inflammation is involved in a host of diseases like rheumatoid arthritis, atherosclerosis, obesity, and even cancer. Several inflammatory mediators are produced and secreted at the time of inflammatory responses such as histamine, serotonin, bradykinins, prostaglandins and other pro-inflammatory mediators (interferons, interleukins, and tumor necrosis factor-α)(Halici et al., 2007). Inflammatory response is a useful process because it provides a conducive physiology to exclude invading pathogens or harmful stimulus. Moreover, the process must be regulated since uncontrolled inflammation is critical for pathophysiological conditions(Chouhan et al., 2020).The most commonly used drug for management of inflammatory conditions are non-steroidal anti-inflammatory drugs (NSAIDs), which have several adverse effects especially gastric irritation leading to formation of gastric ulcers(Patrignani et al., 2011). Therefore, the development of newer and more substantial anti-inflammatory drugs with lesser side effect is necessary. Over the years, medicinal plant have played a significant role with respect to preventing and treating inflammatory conditions, several researchers have reported the anti-inflammatory activity of different parts of combretum species as safer and available anti-inflammatory agent as shown in Table 3.

Table 3: **Anti-inflammatory activities of some combretum species**

Name of plant	Part of plant	Model	Remarks	Ref.
C. glutinosum	Leaf, root and fruit	Inhibition of albumin denaturation and Membrane stabilization test	Significant activity	(Muhammad et al., 2019)
C. collinum	Leaf	TNFα stimulated HaCaT cells	Decreased pro-inflammatory mediators in TNFα stimulated HaCaT cells.	(Marquardt *et al.*, 2020)
C. glutinosum	Leaf	Carrageenan-induced paw edema	Significant inhibitory activity	(Sene et al., 2018)
C. micranthum	Leaf	Carrageenan and acetic acid induced vascular permeability	Significant inhibitory activity	(Olajide et al., 2003)
C. zenkeri	Leaf	egg albumin,	Significant	(Ogbu et al.,

		phospholipase A2 activity and membrane stabilization	inhibitory activity	2020)
C.nioroense	Stem bark	Egg albumin	Significant inhibitory activity	(Akoto et al., 2023)
C.aculeatum	Aerial Parts	carrageenan induced paw edema	Significant inhibitory activity	(Hamad et al., 2019)
C. Platypterum	Leaves	Egg albumin	Significant inhibitory activity	(Uwaya et al., 2022)

CONCLUSION

Combretum genus is one of the genera belonging to the Combretaceae family. Different species of combretum contain flavonoids, terpenoid, steroids, saponins, tannins, and alkaloids which are responsible for the antioxidant and anti-inflammatory potentials of combretum genus. There are several species in this genus which their biological activities and bioactive constituents are yet to explore for therapeutic applications.

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