



A Review on the Chemical Constituents, Anti-inflammatory and Anti-oxidant Agents from Combretum Genus

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JIA and OCO designed the study, wrote the protocol. Authors FKA and TNU wrote the first draft of the manuscript. Authors COU, HNO and FBCO managed the literature searches. All authors read and approved the final manuscript.

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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 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.

1. 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 [1]. 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 [2]. 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 plants play 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 combretaceae family in order to get insight on its therapeutic potentials.

2. 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" [3,4].

"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" [5].

"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" [5].

3. 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
<i>C. molle</i>	Roots, stem bark and leaves	Stomachache, wound healing, edema, skin diseases and gonorrhea	[6] [7]
<i>C. psidioides</i>	Leaves and root	Diarrhea, muscle pain and edema	[7]
<i>C. padoides</i>	Leaves and root	Bloody diarrhea, conjunctivitis, antimalarial, and wound healing	[8,9]
<i>C. sericeum</i>	Leaves, and root bark	Stomach disorder, wound, bone fracture and conjunctivitis,	[10,11]
<i>C. fragrans</i>	Leaves, root and shoots	Leprosy and diarrhea	[12]
<i>C. woodii</i>	Leaves	Abdominal pain, and venereal diseases	[13,12]
<i>C. zeyheri</i>	Leaves and root	Scorpion and snake bites, mental problem, tuberculosis and pneumonia	[14]
<i>C. collinum</i>	Leaves	Earache, rheumatism, diarrhea, cough, and ascariasis	[12,15]
<i>C. paniculatum</i>	Leaves and root	Enlarge spleen and liver, diarrhea, and dysentery	[16]
<i>C. leprosum</i>	Leaves, flowers, stem and root barks	Wound healing, skin rashes, cough and heartburn	[17]
<i>C. erythrophyllum</i>	Leaves, root and stem bark	Abdominal pain, leprosy, venereal diseases, and sores	[18]
<i>C. apiculatum</i>	Leaves	Stomach problems, scorpion stings, disinfect the navel after birth	[19]
<i>C. micranthum</i>	Leaves and roots	colds, fever, measles, bruises colic, vomiting, gastrointestinal problems and malaria	[19,20]
<i>C. imberbe</i>	Leaves and root	Diarrhea, coughs, and toothpaste	[12,19]
<i>C. kraussi</i>	Leaves, root and stem bark	Body pain	[12]

4. PHYTOCHEMISTRY OF SOME COMBRETUM SPECIES

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

5. 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 activities” [21,22]. The genus *Combretum* has yielded mainly pentacyclic triterpenoids varying from oleanolic acid [23,24].

6. 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, chalcones, 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*” [25-27].

7. STILBENES

“Stilbenes are another class of compounds that are part of non-flavonoid polyphenols with 1,2-diphenylethylene as basic structure” [28]. 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 [29-31] including *C. erythrophyllum*, *C. molle*.

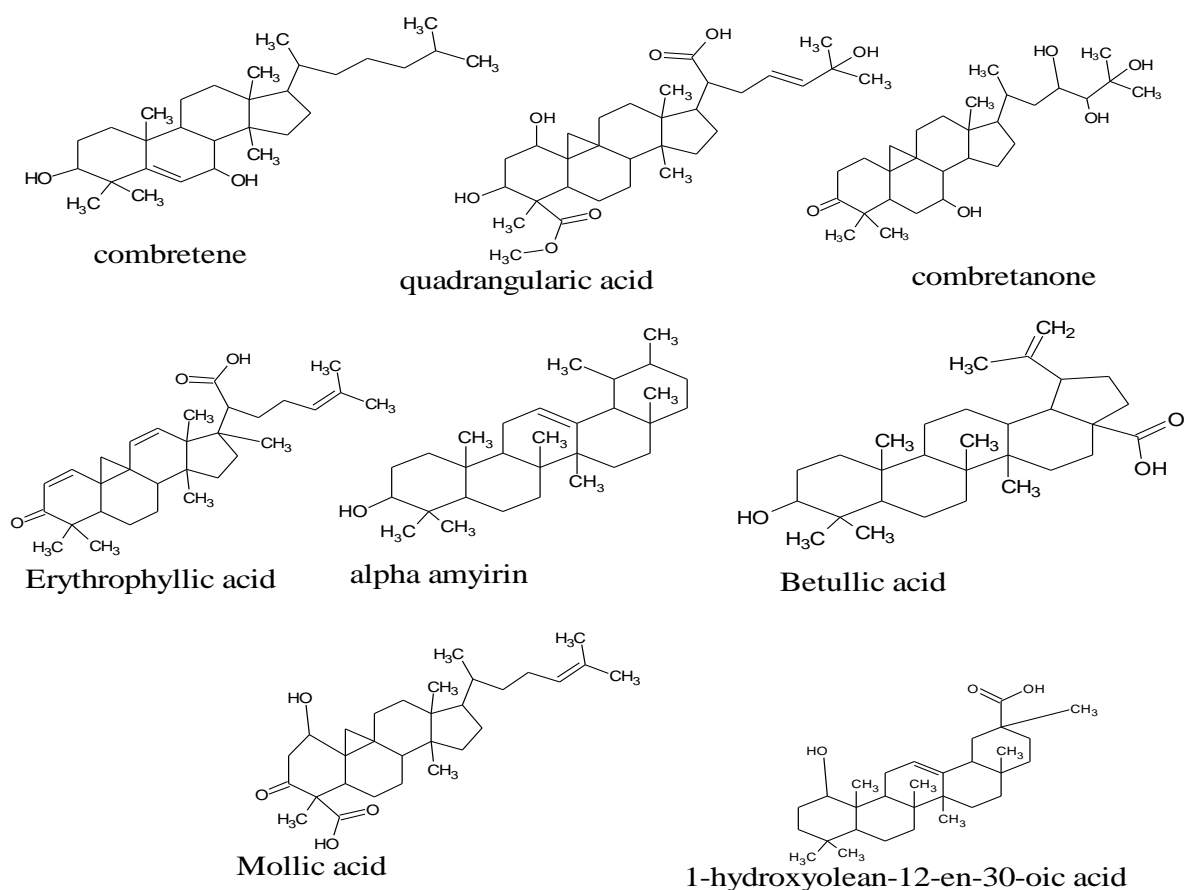


Fig. 1. Structures of terpenoids from some combretum species

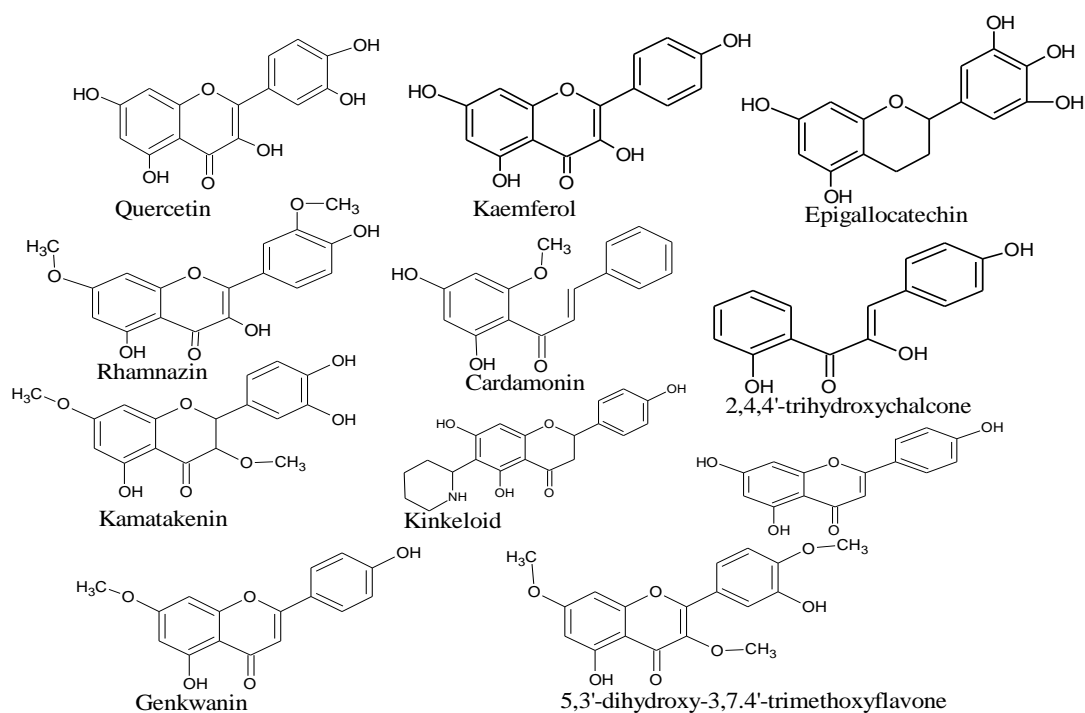


Fig. 2. Structures of flavonoids isolated from some combretum species

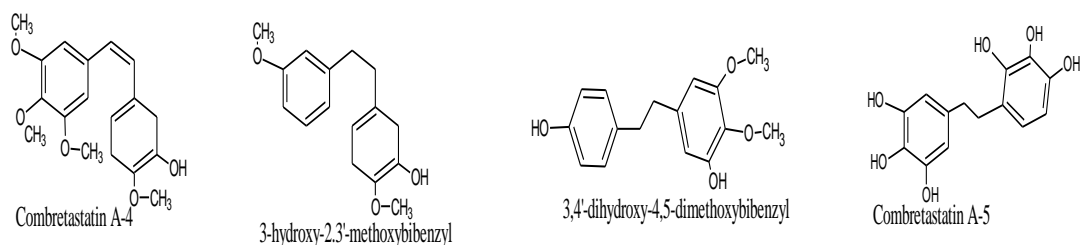


Fig. 3. Structures of stilbenes isolated from combretum species

8. BIOLOGICAL ACTIVITIES OF SOME COMBRETUM SPECIES

Several scientific works 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.

9. OXIDATIVE STRESS

This arises due to inability 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 [32,33]. Antioxidants are 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 [34,35]. 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 [36]. 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 [37,38]. 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 [39]. The antioxidant effect of some combretum species is presented in Table 2.

10. 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 [52]. 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) [53]. 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 [54]. 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 [55]. 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 2. Antioxidant activity of some combretum species

Name of plant	Part of plant	Model	Remarks	Ref.
<i>C. quadrangulare</i>	Leaf	ABTS and DPPH	Significant activity	[40,41]
<i>C. latifolium</i>	Leaf	ABTS and DPPH	Significant activity	[42,43]
<i>C. decondrum</i>	Leaf	ABTS and DPPH	Significant activity	[43]
<i>C. roxburghii</i>	Leaf and stembark	DPPH	Significant activity	[44,45]
<i>C. albidum</i>	Leaf	DPPH	Significant activity	[44,46]
<i>C. quadrangulare</i>	Fruits	ABTS, DPPH, RP and TAC	Significant activity	[40,41]
<i>C. hartmannianum</i>	Leaf	β -carotene–linoleic acid and DPPH	Significant activity	[47]
<i>C. acutum</i>	Leaf	ABTS, FRAP and DPPH	Significant activity	[48]
<i>C. sericeum</i>	Aerial part	ABTS, FRAP and DPPH	Significant activity	[48]
<i>C. niroense</i>	Leaf	ABTS, FRAP	Significant activity	[49]
<i>C. molle</i>	Leaf and Fruit	DPPH, NO and superoxide scavenging assays	Significant activity	[50]
<i>C. paniculatum</i>	Leaf and root	DPPH	Significant activity	[51]

Table 3. Anti-inflammatory activities of some combretum species

Name of plant	Part of plant	Model	Remarks	Ref.
<i>C. glutinosum</i>	Leaf, root and fruit	Inhibition of albumin denaturation and Membrane stabilization test	Significant activity	[56]
<i>C. collinum</i>	Leaf	TNF α stimulated HaCaT cells	Decreased pro-inflammatory mediators in TNF α stimulated HaCaT cells.	[15]
<i>C. glutinosum</i>	Leaf	Carrageenan-induced paw edema	Significant inhibitory activity	[57]
<i>C. micranthum</i>	Leaf	Carrageenan and acetic acid induced vascular permeability	Significant inhibitory activity	[58]
<i>C. zenkeri</i>	Leaf	egg albumin, phospholipase A2 activity and membrane stabilization	Significant inhibitory activity	[59]
<i>C. niroense</i>	Stem bark	Egg albumin	Significant inhibitory activity	[60]
<i>C. aculeatum</i>	Aerial Parts	carrageenan induced paw edema	Significant inhibitory activity	[61]
<i>C. Platypterum</i>	Leaves	Egg albumin	Significant inhibitory activity	[62]

11. 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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