***Review Article***

**Flavonoids Diversity and therapeutic Significance in *Terminalia brownii***

**Abstract**

*Terminalia brownii* species within the family *Combretaceae*, is a widely distributed deciduous tree native to tropical and subtropical regions of Africa, particularly in Eastern and Central parts, including Kenya, Ethiopia, Sudan, and Uganda. Traditionally, various parts of *T. brownii*, including the bark, leaves and roots have been used in folk medicine to manage such as diarrhea, malaria, wound infections, respiratory disorders, and gastrointestinal conditions. The medicinal value of *T. brownii* is largely attributed to its rich profile of secondary metabolites, notably tannins, saponins, alkaloids, phenolics, and flavonoids. Flavonoids such as quercetin, kaempferol and luteolin have been identified in different plant parts, contributing to the plant's antioxidant, antimicrobial, anti-inflammatory and hepatoprotective activities. Despite growing interest in the pharmacological properties of *T. brownii*, comprehensive reviews focusing specifically on the diversity and therapeutic relevance of its flavonoid compounds remain limited. This review aims to bridge that gap by summarizing the classes of flavonoids isolated from different parts of *T. brownii* and highlighting their medicinal applications with a view toward informing future drug discovery and development efforts.

Key words: flavonoids, *Terminalia brownii*, secondary metabolites, natural sources

**1. Introduction**

*Terminalia brownii* is a deciduous medicinal plant of genus *Terminalia* belonging to *Combretaceae* family and is predominantly distributed across sub-Saharan Africa countries such as Kenya, Uganda, Tanzania, South Sudan, Somalia, Ethiopia, Sudan and Democratic Republic of Congo [1,2,3]. They are extensively utilized in herbal medicine for the management of a wide range of health conditions, including wounds, diabetes, kidney disorders, skin diseases, diarrhea, respiratory infection, syphilis, gastric ulcers, back pain, malaria among others [2,4]. Its therapeutic efficacy such as antioxidant, anti-inflammatory, antifungal, antibacterial, antiviral is largely linked to its diverse phytochemical composition, such as triterpenoids, alkaloids, saponin, flavonoids, tannins, and phenolic compounds acids [5]. Among these, flavonoids are considered the principal bioactive constituents contributing to many of the plant’s pharmacological effects [6]. There compounds fall into several subclasses such as flavonols, flavones, flavanones, isoflavones, flavanols, chalcones, anthocyanidins and anthocyanins. Each exhibit unique chemical characteristics and biological effects.

**2. Flavonoids**

Flavonoids constitute a structurally distinct and biologically significant class of plant secondary metabolites that have garnered notable scientific attention due to their extensive range of pharmacological activities and potential therapeutic benefits [7, 8].These polyphenolic compounds are unified by characteristic C6-C3-C6 skeleton (Fig. 1), comprising two aromatic rings (A and B) connected via a three carbon linker that often forms a third heterocyclic ring (C), resulting in a phenylchromane configurations [9].


**Fig. 1 Basic structure of flavonoid**

This fundamental backbone permits extensive structural modifications such as hydroxylation, methoxylation, glycosylation and acylation, which contribute to the vast chemical heterogeneity observed within the flavonoid family [9]. These structural variations significantly impact their solubility, absorption and pharmacological action, including antioxidant, anti-inflammatory, antimicrobial, anticancer and cardiovascular benefits [7, 10]. The pleiotropic bioactivities of flavonoids are mediated through several well characterized molecular mechanism such as direct inhibition of enzymes involved in inflammation and carcinogenesis, modulation of transcription factors altering key signaling pathways and epigenetic regulation through change in DNA methylation and histone modification [11]**.** These mechanisms underlie the therapeutic potential of flavonoids [12]. Flavonoids are categorized into seven main subclasses based on the oxidation state and substitution pattern of the central pyran ring: flavones, flavonols, flavanones, flavanols (or flavan-3-ols), isoflavones, chalcones and anthocyanins [13, 14]. Each subgroup has a unique structure that determine its specific biological role and therapeutic mechanisms [15, 16].

**3. Flavonols**

Flavonols constitute a prominent subclass of flavonoids, characterized by completely oxidized C – ring (Fig. 2), featuring a hydroxyl moiety at the C-3 which may be glycosylated and ketone group at C-4 [14]. Additionally, they possess a conjugated double bond between the C-2 and C-3 position [13].



**Fig. 2 Basic structure of flavonols**

Similar to flavones, flavonols display significant structural diversity in hydroxylation and methylation on their aromatic rings [17]. This variability is further enhanced by the extensive range of glycosylation modifications, which influence their solubility, stability, and bioactivity [18]. Due to this high degree of chemical versatility, flavonols are considered not only one of the most structurally diverse but also the most prevalent subgroup of flavonoids presents in a wide variety of fruits, vegetables and medicinal plants [19]. Some of flavonols isolated from stem bark and leaves of *Terminalia brownii* (Table 1) includes Quercetin-7-O-β-D-glucopyranoside (1), quercetin-7-O-galloyl-glucoside (2), Myricetin-3-rhamnoside (3), Kaemferol-4'-sulfate (4) Fig. 3.



**Fig 3. Examples of Flavonols Isolated from *Terminalia brownii***

Flavonols demonstrate potent antioxidant capabilities by neutralizing free radicals and mitigating oxidative stress, alongside antibacterial, cardioprotective, anticancer, and antiviral effects [20]. Emerging epidemiological evidence suggests that consistent dietary consumption of flavonol-rich foods is linked to a significant reduction in the incidence of gastric cancer, particularly among smokers and women [21, 22]. These findings underscore the potential of flavonols as functional dietary components in cancer prevention and overall health promotion [23, 24].

**4. Flavones**

Flavones are subclass of flavonoids, structurally characterized by their 2-phenylchromen-4-one backbone (Fig. 4) distinguishing them from flavanones [25, 26].



**Fig. 4 Basic structure of flavones**

Flavones are widely distributed across various plant species and are found in fruits, vegetables and herbs. They are particularly abundant in citrus fruits, where they are often glycosylated [27]. These compounds have attracted extensive interest due to their diverse pharmacological profile, encompassing antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic and sedative properties [28, 29]. In plants, flavones play roles in stress responses and signal mediation, while in humans, they serve as nutraceuticals with considerable therapeutic potential [30, 31]. Some of flavones isolated from stem bark, leaves and flower of *Terminalia brownii* (Table 1) includes rhamnetin-3-*O*-(2,3,6-tri-galloyl)-β-D-glucopyranoside (5), Apigenin (6), 5,6-dihydroxy-3',4',7-tri-methoxy flavone (7). Fig. 5. Their multitarget nature underlines their potential as pharmacophores for the treatment of complex ailments such as cancer, metabolic syndromes, neurodegenerative disorders and infectious diseases [32, 33].



**Fig 5. Examples of Flavonols Isolated from *Terminalia brownii***

**5. Flavanones**

Flavanones exhibit structural resemblance to flavones, however, they are distinguished by the absence of a double bond between C-2 and C-3 position of the central ring hence they are classified as dihydroflavones (Fig. 6) [9, 13]. Absence of double bond gives flavanones a chiral center at C-2, resulting in the existence of two potential stereoisomers for each respective compound [34].



**Fig. 6 Basic structure of flavanones**

Citrus fruits such as lemons, grapes and oranges are the main dietary source of flavanones although they are also present in small quantities in some medicinal plants [35]. Their medicinal relevance lies in their antioxidant, anti-inflammatory and antimicrobial capabilities [36]. Naringenin-4'–methoxy-7-arabinoside (8), Naringenin -4'-methoxy-7-pyranoside (9) and 5,7-dihydroxyflavanone (10) (Fig. 7) are some of flavanone derivatives reported from stem bark and flowers of *Terminalia brownii.* These compounds are known to combat bacterial and fungal pathogens and have shown promise as natural therapeutic agents [18]. Flavanones have demonstrated cardioprotective effects by improving blood lipid profiles, enhancing endothelial function and lowering blood pressure [22]. Their ability to modulate enzymes and signaling pathways involved in cancer progression has also attracted interest for their potential use in cancer prevention and treatment [26].



**Fig 7. Examples of Flavanones Isolated from *Terminalia brownii***

**6. Isoflavones**

Isoflavones are a unique subgroup of flavonoids in which the B-ring is attached to the third carbon of the central heterocyclic ring (Fig. 8), distinguishing them structurally from other flavonoids [37]. This unique arrangement gives isoflavones a different substitution pattern and biological profile compared to other subclasses [38, 39].



**Fig. 8 Basic structure of isoflavones**

Isoflavones are predominantly found in leguminous plants like soybeans, where they are present in both aglycone and glycoside forms [40]. In addition to legumes, some non – leguminous plants such as medicinal plants also produces isoflavones [41, 42, 43]. Example of isoflavone isolated from *Terminalia brownii* include 7,4'-dihydroxyisoflavone (11) Fig. 9. In plants, isoflavones aid in microbial communication and act as precursors to phytoalexins while in humans, they mimic estrogenic activity due to their similarity to 17-β-estradiol, enabling them to bind selectively to estrogen receptors, showing a stronger affinity for Erβ over Erα [44, 45]. This enables them to act as phytoestrogens, potentially benefiting conditions like menopause, osteoporosis, and hormone-related cancers [46, 47].

 

 **Fig 9. Examples of Isoflavone isolated from *Terminalia brownii***

Additionally, their antioxidant properties help reduce oxidative stress and DNA damage, contributing to anti-inflammatory and anticancer effects [48]. Despite their limited distribution in nature, isoflavones are of significant interest for their dual roles in plant ecology and human health [49].

**7. Flavanols**

Also referred to as flavan-3-ols or catechins, flavanols are structurally defined by the presence of a hydroxyl group at the C-3 position, lack of carbonyl group at C-4 and absence of double bond between C-2 and C-3 (Fig. 10) [7].



**Fig 10. Basic structure of flavanols**

They are found fruits such as bananas, apples, and also in some medicinal plants [8]. Examples of flavanols isolated from *Terminalia brownii* Catechin (12), Epicatechin (13) Fig. 11.



**Fig 11. Examples of Flavanols Isolated from *Terminalia brownii***

Their antioxidant and free radical scavenging properties help plant mitigate oxidative damage thus supporting overall plant resilience [13, 50]. Flavanols are widely recognized for their potent antioxidant properties [9, 18]. They enhance endothelial function by increasing nitric oxide bioavailability within the vascular system, thereby contributing to vascular protection against oxidative stress induced by tobacco exposure [41]. Regular intake of flavanol rich food has been associated with sustained improvement in endothelial performance and reduced risk of cardiovascular diseases [51].

**8. Chalcones**

Chalcones exhibit structural resemblances to flavones, however they lack heterocyclic ring (C ring) [13, 24]. Conversely, they exhibit an open-chain configuration (Fig. 12), defined by a conjugated double bond connecting the A and B rings [33].



**Fig. 12 Basic structure of chalcones**

This unique structural arrangement imparts to chalcones their distinctive yellow pigmentation [31]. They possess strong antioxidant, anti-inflammatory, antimicrobial, anticancer and antidiabetic activity by improving insulin sensitivity enhancing glucose uptake and inhibiting enzymes like α-glucosidase and α-amylase involved in carbohydrate metabolism [30]. 2',6',4-trihydroxy-3'-methoxy-4-O-prenyloxy chalcone (14) is an example of chalcone isolated from *Terminalia brownii* leaves (Fig. 13) [50].



**Fig 13. Examples of chalcones Isolated from *Terminalia brownii***

**9. Anthocyanins and anthocyanins**

Anthocyanins and anthocyanidins constitute a distinctive subclass of flavonoids that account for the red, purple and blue pigmentation observed in various flowers and fruits [53]. Anthocyanins, the glycosylated form of anthocyanidins are structurally similar to flavonols, characterized by the absence of C-3 hydroxyl group and have a positively charged anthocyanidin nucleus, which is responsible for their coloration [54]. These flavonoids possess multiple therapeutic properties including antimicrobial, anti-inflammatory, antidiabetic, antioxidant activity that helps reduce cellular oxidative stress and may play a role in preventing diseases like cancer, cardiovascular disorders and neurodegenerative conditions [55, 56]. Literature review mining revealed scanty information on anthocyanins and anthocyanidins isolated from *Terminalia brownii*.

**Medicinal uses of Terminalia brownii**

*Terminalia brownii* has been utilized extensively in traditional therapies in many African countries with different components of the plant used in alleviating a diverse array of illnesses [2, 57]. Stem bark and roots decoctions are orally administered to treat malaria, diarrhea, dysentery, cold, fevers, diabetes, tuberculosis, syphilis and stomach disorders [3, 58]. Stem bark is chewed as remedy for cough, toothaches and gum infections, infusion of stem bark and roots are mixed with meat soup or porridge to treat hepatitis while wood ash are used as disinfectant in treatment of wound [59]. Root infusions are traditionally used to manage reproductive health issues such as menstrual disorders and postpartum complications [60].

 In vivo studies have studies have validated its antimalarial activities: 80% methanol bark extract achieved 60% Chemosuppression against *Plasmodium berghei* in mice supporting the folkloric use [61]. According to [3]**,** methanolic crude extract of stem bark recorded significant anti-hyperglycemic activity in streptozotocin induced diabetic mice. The activity of *T. brownii* stem bark is attributed to presence of secondary metabolites such as flavonoids (Table 1) which includes Quercetin-7-O-β-D-glucopyranoside, Quercetin-7-O-galloyl-glucoside and naringenin derivatives accounts for these biological activities. For example, quercetin-7-O-galloyl-glucoside combines antioxidant moieties from both quercetin and gallic acid, effectively reducing oxidative stress and related diseases such as like Alzheimer´s, cardiovascular disorders and cancer [62,63].

The leaves of *T. brownii* are used in treating eye infections, fungal skin conditions such as ringworm and gastrointestinal disorders such as diarrhea, colic and gastric ulcers [64]. Pharmacological studies have validated some of these traditional uses. Methanolic leave extract have demonstrated significant antibacterial activity against *streptococcus pneumoniae* with zone of inhibition comparable to convectional antibiotic [65]. Ethyl acetate, methanol and acetone crude extract of *T. brownii* leave have demonstrated strong antifungal, anti-inflammatory and antipyretic properties attributed to high concentration of flavonoid glycoside such as luteolin-7-O-glucoside, apigenin [6]. The antioxidant activity is attributed to the polyphenolic content in the leaves further supporting their use in mitigating oxidative stress – related condition [66].

Table 1: Flavonoids isolated from *Terminalia brownii*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S/No.** | **Flavonoids** | **Class**  | **Plant part**  | **Solvent**  | **Medicinal use** | **Reference** |
| 1 | Quercetin-7-O-β-D-glucopyranoside | Flavonol | Stem bark  | Ethyl acetate | Antifungal | [67]  |
| 2 | quercetin-7-O-galloyl-glucoside | Flavonol  | Stem bark | Ethyl acetate | Anti-inflammatory, anticancer | [68]  |
| 3 | Quercetin | Flavonol | Stem bark | Methanol | Antidiabetic, antimicrobial  | [68]  |
| 4 | Quercitin 7-O-β- diglucoside | Flavonol | Stem bark | Ethyl acetate | Antioxidant, anticancer | [67] |
| 5 | Naringenin | Flavanone | Stem bark | Methanol | Anti-inflammatory, antidiabetic  | 69]  |
| 6 | Naringenin 4’methoxy-7- arabinoside | Flavanone | Stem bark | Ethyl acetate | Antimicrobial, anti-inflammatory  | [6] |
| 7 | naringenin-4'-methoxy-7-pyranoside | Flavanone | Stem bark | Ethyl acetate | Antimicrobial  | [68] |
| 8 | 5,7-dihydroxyflavanone | Flavanone | Stem bark | Ethyl acetate | Antioxidant, anti-inflammatory  | [67] |
| 9 | 5,6-dihydroxy-3',4',7-tri-methoxy flavone | Flavone | Stem bark | Ethyl acetate | Antimicrobial’, anticancer  | [6] |
| 10 | 7-hydroxy-3-[6'-hydroxyphenyl-2'-oxo-ethyl]chromone | Flavone | Stem bark | Water  | Neuroprotective and hepatoprotective effects | [70]  |
| 11 | Apigenin | Flavone | Leaves  | Ethyl acetate  | Antioxidant, anti-inflammatory | [6] |
| 12 | Apigenin 7-O-methyl ether | Flavone | Leaves | Ethyl acetate | Anticancer, antimicrobial  | [67] |
| 13 | Luteolin | Flavone | Leaves | Ethyl acetate  |  Anti-inflammatory  | [6] |
| 14 | Luteolin-7-O-glucoside | Flavone | Leaves  | Ethyl acetate | Anticancer, anti-inflammatory | [6] |
| 15 | Kaemferol-4'-sulfate  | Flavonol | Leaves  | Ethyl acetate | Antimicrobial | [6] |
| 16 | Myricetin-3-rhamnoside | Flavonol | Leaves  | Ethyl acetate | Antioxidant, antimicrobial  | [6] |
| 17 | Quercetin-7-β-O-di-glucoside | Flavonol | Stem bark | Ethyl acetate | Ant-plasmodial activity  | [67] |
| 18 | Quercetin-7-O-galloyl-glucoside | Flavonol | Stem bark | Ethyl acetate | Antifungal, antibacterial  | [67] |
| 19 | 7,4'-dihydroxyisoflavone | isoflavone | Stem bark | Chloroform | Antioxidant, antimicrobial  | [71]  |
| 20 | 7,3'-dimethoxy quercetin rhamnoglucoside  | Flavonol | Leaves  | Chloroform | Anticancer, anti-inflammatory  | [70] |
| 21 | Kaempferol 7-methoxy-3-sulphate |  | Leaves  | Chloroform | Antioxidant, antimicrobial  | [70]  |
| 22 | 2’,6’,4-trihydroxy-3’-methoxy-4-O-prenyloxy chalcone | chalcone | Leaves  | Methanol | Anti-inflammatory, anticancer  | [52] |
| 23 | rhamnetin-3-*O*-(2,3,6-tri-galloyl)-β-D-glucopyranoside | Flavone  | Flower | 50%DCM/MeOH | Antidiabetic, antibacterial  | [72] |
| 24 | 3,3',4',5 tetrahydroxy-7-methoxy flavone | Flavone  | Flowers | 50%DCM/MeOH | Anti-inflammatory, anticancer | [72] |
| 25 | Myricetin-3-rhamnoside | Flavonol | Leaves  | Ethyl acetate | Antioxidant, anticancer  | [6] |
| 26 | 3,3',4',5,7-pentahydroxyflavone | Flavone  | Flowers  | 50%DCM/MeOH | Antimicrobial, antioxidant  | [71]  |

**Conclusion**

*Terminalia brownii* stands out a valuable medicinal plant within the Combretaceae family with a broad distribution across African region and strong foundation in traditional medicine. Its rich reservoir of secondary metabolites, particularly flavonoids such as quercetin, kaempferol and luteolin, contributes to plant´s antimicrobial, antioxidant and anti-inflammatory actions. The correlation between its ethnomedicinal uses and phytochemical constituents underscores its potential for further scientific exploration. Continued research into its bioactive compounds, mechanism of action and clinical relevance is essential for validating traditional claims and advancing its integration into modern health care.

**Conflict of interest**

The authors declare no conflict of interest.

**Disclaimer (Artificial intelligence)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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