

## Antioxidant Activity of a Triterpene Isolated From the Methanolic Leaf Extract of *Ficus Vogelii*

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### ABSTRACT

Oxidative damage is an important factor identified in the pathogenesis of many life-threatening diseases. This study investigated the antioxidant activity of some plant parts of *Ficus vogelii* (African Fig) and isolated its possible antioxidant phytoconstituents. Antioxidant activity of the methanol extract of *Ficus vogelii* stem bark, fruit, leaf and root bark were evaluated using 2, 2-diphenyl-1-picrylhydrazyl radical scavenging activity (DPPH), Lipid Peroxidation (LPO), ABTS (2, 2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid), superoxide ion, nitric oxide and ferric reducing antioxidant power (FRAP). The most active extract was subjected to chromatographic separation to isolate its chemical constituent using silica gel and Sephadex LH-20. The leaf extract elicited the best antioxidant activity with DPPH (25.46 mg/ml), FRAP (253.54±7.35 µg/ml), ABTS (28.45 mg/mL), Superoxide radical scavenging (57±3.56 µg/ml), NO (35.45±3.71 µg/ml) and MDA (23.97 mg/mL). The purification process led to the isolation of compound **1** ((Z)-2-hydroxy-4,4,7b,12,12-pentamethyl-11-(5-(4,5,6-trihydroxy-2-methylcyclohex-2-en-1-yl)pent-2-en-2-yl)-4,4a,5,6,6a,7,7a,7b,8,9,10,11,11a,12,13,13a,14,14a octadecahydrobenzo[k]tetraphen-3(2H)-one. The isolate elicited excellent antioxidant property which further justified the activity obtained for the methanol leaf extract. The HOMO and the LUMO analysis revealed the phytoconstituent is susceptible to charge transfer.

**Keywords:** *Ficus vogelii* (Moraceae), Polyhydroxylated terpenoid, Molecular Orbital Analysis, Antioxidants, Structural Elucidation.

### Introduction

Free radicals and Reactive-oxygen species (ROS) and are key inducers identified in cellular and tissue damages that results to diabetes, cancer, inflammation and other life-threatening ailments (Oyinloye *et al.*, 2015). Antioxidants are molecules that provide the vital protection to cells and tissues by scavenging free radicals produced from stress and other hectic activities (Nithiyanantham *et al.*, 2012 Goutam *et al.*, 2018).

They also protect from arrays of lipid peroxidation, DNA strand breaking and all body protein damages usually caused by rapid production of ROS (Juan *et al.*, 2021).

The use of plants as source of medicine by traditional practitioners and people living with diverse kinds of ailment is widespread (Maroyi, 2011). These plants are proven to have natural antioxidants that can effectively scavenge free radicals and ROS generated in the body (Akbari *et*

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al., 2022). Hence, it may be a source of new antioxidant agent that can be developed to novel drugs (Shaikh *et al.*, 2014).

*Ficus vogelii* (Moraceae), is a fig tree commonly found in Africa. Its whose fruits are important food resources for animals like monkeys, birds and many frugivorous invertebrates (Kalko *et al.*, 1996). Diverse plant parts: fruits, leaves, root-bark and stem-bark are depleted for therapeutic purposes (Abegaz *et al.*, 2000, Igile *et al.*, 2015). In traditional medicine, the leaves of *Ficus vogelii* are explored for treating stomach ulcers, asthma, burns, dysentery, anemia, infections, as well as different endocrine complications (Sirisha *et al.*, 2010). The extracts of *Ficus vogelii* roots has been investigated for their anti-ulcerogenic, antidiabetic, antianemia and antihepatotoxic activities (Egbuna *et al.*, 2011; Ao *et al.*, 2008). Despite the pharmacological activities performed on various solvent extracts of *Ficus vogelii*, the antioxidant potential of its morphological parts is yet to be investigated. Herein, we investigate the antioxidant activities of the various morphological parts of *Ficus vogelii*. The study also isolated an antioxidant compound from the most active crude extract of the plant.

## Materials and Methods

### General

The <sup>1</sup>H and <sup>13</sup>C NMR, as well as 2D, spectra were taken on a Bruker Avance DRX 500 NMR spectrometer using TMS as internal standard. EIMS was performed on a Bruker APEXII mass spectrometer. Column chromatography was carried out on Merck silica gel (200–400 mesh), and the HF254 silica gel for TLC was provided by Sigma Co. Ltd. Sephadex LH-20 (18–110 cm) was obtained from Pharmacia Co. All chemicals and reagents were obtained from Sigma-Aldrich, BioBasic, or Fisher Scientific.

### Plant collection, extraction and isolation

The leaves, fruits, stem bark and root bark of *Ficus vogelii* were collected in Abeokuta metropolis.

The collected morphological parts were identified, authenticated and deposited at the Faculty of Pharmacy Herbarium, OAU, Ile-Ife, with voucher specimen number FPI 2072. Isolation of the antioxidant compound was as previously described (Ayodele *et al.*, 2024).

### Anti-Oxidant studies

#### 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity (DPPH•)

The free radical scavenging activity of the extracts and isolate were measured using 2, 2-diphenyl-1-picrylhydrazyl (DPPH•) method described by Manzocoo *et al.* (1998). DPPH solution was prepared by dissolving 0.01 g of DPPH powder in 100 mL of methanol. Gradient concentrations (100-1500/mL) of the plant extract and (100-1000 /mL) of the standard drug (ascorbic acid) was prepared while 1mL of each of them were added into well labeled and arranged test tubes. This was followed by the addition of 3 mL of DPPH solution and the resulting mixture was incubated for 30 mins in the dark at room temperature after which the absorbance was determined at 570 nm using methanol as the blank.

#### Inhibition of Lipid Peroxidation (LPO)

LPO of the extracts and isolate carried out according to method described by Ibrahim *et al.* (2012). Fresh liver sample of cow was purchased from an abattoir in Omida market Abeokuta, Ogun state. It was weighed and homogenized to get a clear homogenate in a cold phosphate buffer (pH=7.4) using a pestle and mortar. 1 mL of the liver homogenate was added to the different concentrations of the plant extract (100 - 1500 µg/mL) prepared inside well labeled test tubes. Lipid peroxidation began with the introduction of 100 µL of a reaction mixture. The reaction mixture contained 1.5 mheL of 0.67% Thiobarbituric Acid (TBA) in 50% acetic acid. The resulting mixture was incubated in a water bath at 80°C for 30 mins. The intensity of the pink

coloured complex formed was measured in a spectrophotometer at 535 nm.

#### **ABTS (2, 2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) scavenging activity**

The ABTS assay was performed according to the method described by Avallone *et al.* (2000). Mixture of 3 g/L of ABTS and 132 g/mol NH<sub>4</sub>SO<sub>4</sub> in ratio 1:1 was left to stand at room temperature for 12 hours in the dark before use. To different concentrations (100–1500 µg/mL) of the extract, 0.6 mL of the mixture of ABTS and NH<sub>4</sub>SO<sub>4</sub> was added, followed by the addition of 0.4 mL ethanol. Finally, the absorbance was recorded at 745 nm.

#### **Reducing power scavenging activity**

Reducing power activity was determined by the method described by Jimoh *et al.* 2020. Plant extracts and isolate (2mL) were mixed with 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL of 1% potassium ferricyanide (10 mg/mL). The mixture was incubated at 50°C for 20 minutes, then rapidly cooled, mixed with 2.5 mL of 10% Trichloroacetic Acid (TCA) and centrifuged at 6500 rpm for 10 minutes. 2.5 mL of supernatant was diluted with distilled water (2.5 mL) and then ferric chloride (0.5 mL, 0.1%) was added and allowed to stand for 10 minutes. The absorbance was read spectrophotometrically at 700 nm.

#### **Nitric oxide scavenging activity**

Nitric Oxide (NO) radical scavenging activity of the plant extracts and isolate was determined by the method described by Duru and Nbata, (2010). Sodium Nitroprusside (1.5 mM) in phosphate buffered saline was mixed with various concentrations of the plant extracts and isolate (100-1500 µg/mL) dissolved in methanol and incubated at 25°C for 5 hours at room temperature. After 5 hours incubation, 1.5 mL of the incubated solution were removed and diluted with 0.5 mL of Griess reagent. The absorbance was determined at 546 nm.

#### **Superoxide scavenging activity (SO)**

Superoxide scavenging assay was carried out according to the method described by Manzocoo *et al.* (1998). Plant extract (0.5mL) was taken at different concentrations (100-1500 µg/mL), to the extracts and isolate 1 mL of Dimethyl Sulphoxide (DMSO) was added then 0.2 mL nitroblue tetrazolium (NBT) was also added. The solutions were prepared in 0.1M sodium phosphate buffer (pH 7.4). The absorbance was read at 540 nm and then 560 nm.

#### **Result**

Studies have shown that *Ficus vogelii* leaf extract is a very good natural antioxidant that has been in use as alternative herbal medicine because it is good in fighting reactive oxygen species (ROG) production and also can resist lead reproductive toxicity (Ezugworie and Uchewa, 2019). *Ficus vogelii* as a vegetable that contains antioxidants which can be taken through diet to maintain the homeostasis between free radicals and antioxidants and thus prevent various deleterious effects, like lead toxicity, inflammation, cancer, aging, cardiovascular and brain disorders (Willcox *et al.*, 2004 and Wadood *et al.*, 2013).

The crude extract of the stem bark, leaf, fruits and root bark of *Ficus vogelii* was assayed to establish their antioxidant property and also identify the most active morphological plant part. The obtained results in the ABTS, DPPH, SO, LPO, NO and FRAP assays are presented below.

All the extracts showed good scavenging activities against the DPPH radical. The extract of the leaf elicited the highest DPPH radical scavenging activity (25.46 mg/ml) followed by the stem bark (26.23 mg/ml). The root bark (73.54 mg/ml) and fruit extract (52.58 mg/ml) showed moderate scavenging activity. The lower the value obtained for DPPH radical scavenging assay, the stronger its antioxidant potential (Lue *et al.*, 2010). The results further revealed that the plant leaf has more chemical constituent that are capable of donating

hydrogen atoms, as compared to the stem bark, fruit and root bark extract.

In this study, the ferric reducing antioxidant power (FRAP) assay reveals that the leaf extract (253.54±7.35 µg/ml) elicited a FRAP activity ((253.54±7.35 µg/ml) which is followed by the

root bark (307.23±2.30 µg/ml), stem bark (317.62±0.92 µg/ml) and fruit (432.34±1.62 µg/ml) extract activities. The result showed that the extract possesses reductones that is capable of donating hydrogen atom to break the free radical chain.

**Table 1:** Antioxidant Results of the Morphological Parts of *Ficus Vogelii*

Extract compounds	NO (µg/ml)	Superoxide Ion (µg/ml)	DPPH IC <sub>50</sub> (mg/ml)	ABTS IC <sub>50</sub> (mg/ml)	MDA IC <sub>50</sub> (mg/ml)	FRAP (µg/ml)
MLEFV	35.45±3.71 <sup>a</sup>	57±3.56 <sup>a</sup>	25.46	28.45	23.97	253.54±7.35 <sup>a</sup>
MSEFV	42.19±7.21 <sup>a</sup>	256±11.21 <sup>a</sup>	26.23	31.78	31.78	317.62±0.92 <sup>b</sup>
MREFV	105.34±10.71 <sup>a</sup>	1521±30.46 <sup>a</sup>	73.54	46.63	67.05	307.23±2.30 <sup>b</sup>
MFEFV	68.14±7.51 <sup>a</sup>	784±7.89 <sup>a</sup>	52.58	39.70	37.72	432.34±1.62 <sup>b</sup>
Catechin	36.81±4.34 <sup>a</sup>	225±10.89 <sup>b</sup>	34.13	36.32	27.69	310.44±6.73 <sup>b</sup>

Data are expressed as mean ± SD (n=2)

**DPPH** -2, 2-diphenyl-1-picrylhydrazyl radical scavenging activity, **MDA**: Malonaldehyde (index of lipid peroxidation), **NO**: Nitric oxide, **MLEFV**: Methanolic leaf extract of *Ficus vogeli*, **MSEFV**: Methanolic stem extract of *Ficus vogeli*, **MREFV**: Methanolic root extract of *Ficus vogeli*, **MFEFV**: Methanolic stem extract of *Ficus vogeli*, **IC<sub>50</sub>**: Inhibitory concentration at 50µg/ **ABTS**: -2, 2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid

The ABTS assay is a reproducible method that is used to investigate the radical scavenging power of chemical constituents and extracts of plant materials, whereby the antioxidant compounds of the extract donates hydrogen atom to obtain a non-radical molecule (Gangwar *et al.*, 2014). The methanolic leaf extract of *F. vogelii* elicited the strongest ABTS radical scavenging activity with maximum activity of 28.45 mg/ml, followed by the stem bark (31.78 mg/ml), fruit (37.72 mg/ml) and root bark (67.05 mg/ml).

Superoxide anion is a radical that is harmful to the cellular components of body organs. Polyphenols are powerful antioxidants that effectively scavenge superoxide anions (Dhanasekaran, 2020). The leaf extract elicited the best superoxide anions scavenging property at IC<sub>50</sub> of 57±3.56 mg/ml. The stem bark showed the second-best superoxide

anion scavenging potency at 256±11.21 mg/ml followed by fruit extract (784±7.89 mg/ml) and root bark (1521±30.46 mg/ml). The good superoxide anion scavenging activity of the leaf as compared to catechin (225±10.89 mg/ml) may be attributed to the abundance of polyphenolics in its methanolic extract.

Nitric oxide inhibition is important in preventing inflammation and changes that occurs in tissues. Hence, a potent NO inhibitor is capable of preventing inflammation related diseases (Sharma *et al.*, 2007). In this study, the leaf extract (35.45±3.71 mg/ml) elicited the best NO inhibition property as compared to catechin (36.81±4.34 mg/ml). The NO inhibitory activity of other morphological parts is ranked in order of stem bark (42.19±7.21 mg/ml), fruit (68.14±7.51 mg/ml) and root bark (105.34±10.71 mg/ml).

The changes in cell permeation, inhibition of metabolic processes, ion transport modification results from the disturbance in cell membrane assemblage. These cause the formation of reactive oxygen species that aggregate during lipid peroxidation (Lai *et al.*, 2021). All extracts tested in the study showed excellent potential of preventing MDA formation. The leaf extract ( $IC_{50}=23.97$  mg/mL) elicited the best MDA inhibition as compared to the standard (27.69 mg/mL). The activity of the leaf extract is closely followed by stem bark (31.78 mg/mL), fruit (37.72 mg/mL) and root bark (67.05 mg/mL).

### Structural elucidation of compound 1

Compound 1 (45 mg) was isolated as a ash amorphous solid; m.p 229 °C, TOF MS ES<sup>+</sup>  $m/z$  = 609.45 [M+1]<sup>+</sup>. The <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta_H$ : 1.10 (3H, s, Me-23), 1.05 (3H, s, Me-24), 1.03 (3H, s, Me-25), 0.94 (3H, s, Me-26), 0.74 (3H, s, Me-27), 0.96 (3H, s, Me-28), 1.77 (3H, s, Me-30), 4.77 (2H, s, H-31). The <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 41.9 (C-1), 27.4 (C-2), 79.0 (C-3), 37.1 (C-4), 55.1 (C-5), 18.4 (C-6), 21.6 (C-7), 50.3 (C-8), 55.1 (C-9), 37.3 (C-10), 23.9 (C-11), 54.9 (C-12), 49.6 (C-13), 21.6 (C-14), 41.6 (C-15), 54.8 (C-16), 44.7 (C-17), 27.3 (C-18), 46.7 (C-19), 39.3 (C-20), 34.2 (C-21), 21.6 (C-22), 26.9 (C-23), 21.0 (C-24), 16.1 (C-25), 15.7 (C-26), 16.4 (C-27), 16.1 (C-28), 148.6 (C-29), 25.4 (C-30), 110.1 (C-31). FTIR (KBr,  $\nu$ , cm<sup>-1</sup>): 2922, 2855, 1700, 1438 and 1371 cm<sup>-1</sup>

Compound 1 was isolated as an ash amorphous material. The <sup>1</sup>H NMR (400 MHz, DMSO) showed proton signals at  $\delta_H$ : 5.23 (1H, d,  $J=8.0$  Hz), 5.16 (1H, s), 4.77 (1H, d,  $J=7.5$  Hz), 4.57 (1H, s), 4.44 (1H, t), 4.31 (1H, s), 4.28 (1H, t), 3.62 (1H, m), 3.10 (1H, m), 2.73 (1H, d,  $J=9.68$  Hz), 1.86 (2H, s), 1.23 (1H, s), 1.07 (3H, s), 0.98 (3H, s), 0.86 (3H, s), 0.74 (3H, t) and 0.68 (3H, s). A characteristic doublet of doublet signal observed at  $\delta_H$  2.831 and found to have a long correlation in the HMBC spectrum with the carbon signals at  $\delta_C$ : 148.5, 122.3, 54.9, 44.7, 25.0 allowed the

establishment of the 2-methyl prop-1-enyl substituent and its attachment on carbon 19. The olefinic signal at  $\delta_H$ : 5.27 ( $\delta_C$ 122.3) had a cross peak with the methylene signal at  $\delta_H$ : 1.89 ( $\delta_C$ 23.4). This methylene proton signal was also coupling with the methylene proton signals at  $\delta_H$  1.52 and 1.37 ( $\delta_C$ 18.9). Compound 1 as shown below is therefore identified as (Z)-2-hydroxy-4,4,7b,12,12-pentamethyl-11-(5-(4,5,6-trihydroxy-2-methylcyclohex-2-en-1-yl)pent-2-en-2-yl)-4,4a,5,6,6a,7,7a,7b,8,9,10,11,11a,12,13,13a,14,14a-octadecahydrobenzo[k]tetraphen-3(2H)-one.

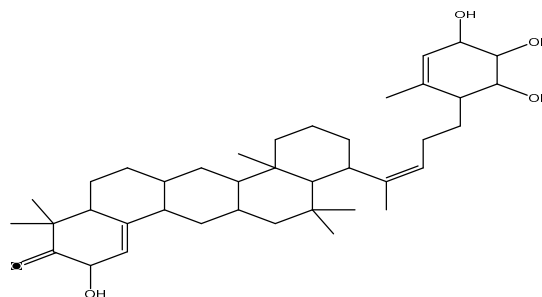
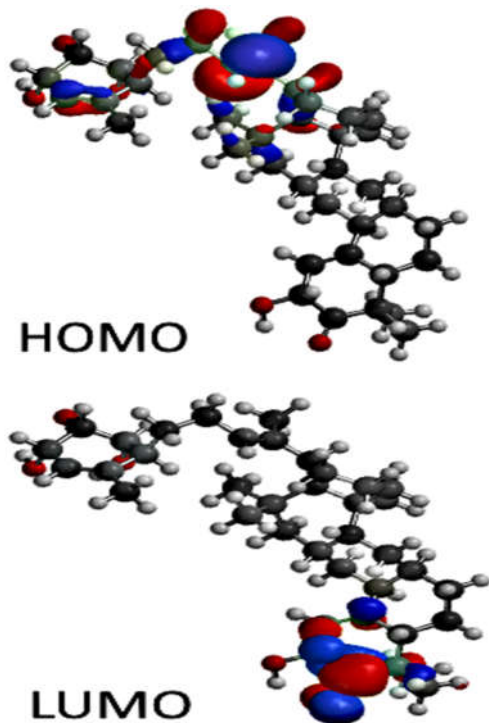


Fig. 1: Chemical structure of 1

### Discussion

The antioxidant potential of the compound was investigated using the models adopted for the extracts. The compound elicited higher antioxidant potential when compared with the antioxidant activity of the leaf and other morphological parts of *F. vogelii*. The DPPH radical scavenging assay of the isolated compound gave  $IC_{50}=7.30$  mg/ml, ABTS (12.25 mg/ml), FRAP (65.34±1.63  $\mu$ g/ml), Superoxide ion (53±3.47  $\mu$ g/ml), NO (9.50±0.61  $\mu$ g/ml) and MDA (18.22 mg/ml). The isolate showed considerably high antioxidant activity when compared with the standard (catechin). The good antioxidant activity of the isolate may be attributed to the presence of hydroxyl groups (Sudha and Srinivasan, 2014). On comparison with Isoviteixin (Ajayi *et al.*, 2017), Isoviteixin exhibited lower DPPH, FRAP and NO scavenging activity than 1. Also, Erenler *et al.*, 2017 reported that the ABTS scavenging activity of ferulic acid ( $IC_{50}$  13.8  $\mu$ g/mL) is lower when compared with 1.

The Frontier molecular orbital of the antioxidant compound was also examined in this study being an efficient parameter used in predicting the highly reactive regions of chemical compounds (Owoseeni *et al.*, 2022). The fundamental descriptors firstly generated *in silico* were the Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) which play significant roles in predicting the chemical reactivity of phytochemicals (Awotuya *et al.*, 2022). The HOMO gives information about the electron-rich orbital and also possesses the potentials to transfer electrons to the unoccupied orbital (Ayeni *et al.*, 2020). The LUMO is an orbital that doesn't have electrons and therefore can accept electrons from the occupied orbitals (Miar *et al.*, 2021). The HOMO and LUMO distribution of **1** is showed in Fig. 2. The molecule gave a HOMO value of -6.17 eV, signifying that it has the tendency to donate electrons. Also, a LUMO value of -0.68 eV showed that the molecule has a good electron accepting tendency.



**Fig. 2:** HOMO and LUMO diagram of compound **1**

Also, the quantum chemical calculations of the isolated antioxidant compound like energy gap ( $\Delta E_{\text{gap}}$ ) ionization potential (I), electron affinity (A), chemical potential ( $\mu$ ), hardness ( $\eta$ ), softness (S), electronegativity ( $\chi$ ) and electrophilicity ( $\omega$ ) was performed to understand the molecular reactivity and stability of the phytochemical. The energy gap of a molecule reveals its kinetic stability property (Owoseeni *et al.*, 2022; Lu *et al.*, 2022). A higher energy gap corresponds to a higher chemical stability while a small energy gap is associated to a high reactivity. **1** had an energy gap value of 5.49 eV, signifying the compound is stable. The ionization potential and electron affinity reveal the energy required to remove and accept electron by a chemical compound (Famuyiwa *et al.*, 2022). **1** had 0.68 and 6.17 eV which showed that it has greater tendency to remove and accept electron.

The hardness and softness are vital descriptors used to study the behaviour of a phytochemical in chemical reactions (Noureddine *et al.*, 2021). A hard molecule shows higher resistance to the changes that may occur in electronic distribution during reaction while softness is the reverse. **1** gave a calculated hardness value of 2.75 eV, while the softness value obtained was 0.36 eV. This signifies that **1** has the tendency to easily partake in chemical reactions.

The chemical potential of a molecule indicates its ability to donate electron. Hence, a less negative chemical potential value corresponds to an of electron donation while a positive chemical potential indicates a lesser electron donating capacity (Schultz *et al.*, 2023). **1** gave a calculated chemical potential value of -2.75 eV, indicating that it has good electron donating property. Electrophilicity of a molecule shows its ability to accept electron. Hence, a higher electrophilicity value indicates its ability to accept electron, also the higher its ability to bind to protein implicated in disease pathophysiology, thereby eliciting good biological activity (Abbass *et al.*, 2022). The

isolated phytochemical gave a moderate electrophilicity value of 1.38 eV, showing that a good antioxidant activity will be obtained. An electronegativity value of 2.75 eV was obtained, suggesting that the compound has tendency to accept electrons.

### Conclusion

The study was designed to evaluate the antioxidant property of extracts of the morphological parts of *Ficus vogelii* using different *in vitro* antioxidant methods. The leaf extract exhibited the best radical scavenging activity in the DPPH, FRAP, superoxide ion, NO, MDA and ABTS assays. Further purification of the leaf extract led to the isolation of **1**. The antioxidant activity of the isolated compound proved it is among the antioxidant compounds present in the plant extract. The HOMO-LUMO energy gap and electrophilicity index of **1** revealed it as a potential bioactive compound. The findings from this work warrant further purification processes to isolate more antioxidant compounds from *Ficus vogelii*.

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### Conflict of Interest

The Authors declare there are no conflicting interest in this work.

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