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Review Article

Chemical Constituents and Biological Activities of *Ficus tikoua* Bureau

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Ficus tikoua Bureau (*F. tikoua* Bur.) is a perennial woody vine in the *Moraceae* family that has been used as a traditional folk medicine for centuries to treat many diseases such as chronic bronchitis, diarrhea, dysentery, rheumatism, and other inflammation-related diseases in certain parts of China, India, Vietnam, and Laos. This medicinal plant contains beneficial secondary metabolites belonging to various chemical classes, including flavonoids, phenolics, terpenoids, steroids, coumarins, and alkaloids. In this review, we have summarized the natural compounds isolated from *F. tikoua* Bur. and their biological effects.

1. Introduction

The growing scourge of communicable and noncommunicable diseases (cancer, diabetes, cardiovascular disease, and chronic lung disease) and the need to find suitable drugs against them are a great challenge to scientists and the society. Similarly, the rising instances of antibiotic-resistant superbugs have made some existing antibiotics ineffective and obsolete. A large population worldwide is afflicted with these diseases, which is causing a great loss of human lives and burden on the economy. Tackling this problem demands science to be one step ahead by researching new drug molecules against such diseases. In this endeavor, plants with their rich diversity of natural compounds have emerged as an option for developing new and promising therapeutic agents and drugs that can act against diseases, with little or no side effects.

Despite the current popularity of synthetic chemistry for the drug development, the application of plants for treating and preventing diseases is in no way less significant [1]; for example, 11% of all the drugs that come under the World Health Organization's essential category is of plant origin [1]. The importance of natural resources in drug development can be understood by the fact that, over a period of 40 years from 1981 to 2020, up to 50% of the approved drugs come from natural products including plants [2]. Plants have been used since time immemorial for their properties. Many plant-derived medicines have been utilized in the treatment of multiple diseases. Plant-derived compounds have shown encouraging results in surmounting antibiotic resistance in pathogenic bacteria [3]. Further, a report studied 122 plant-derived drugs and found that, out of these drugs, 80% had already related to their original ethnomedical and ethnopharmacological purpose, thus emphasizing the importance of traditional folk medicinal plants in the modern medicine [4]. Plant products are also increasingly being used in the cosmetic industry as an ecofriendly alternative to the synthetic ingredients [5–7]. *Ficus tikoua* Bureau (*F. tikoua* Bur.) is one such ethnomedicinal plant that is commonly found in China, India, Vietnam, and Laos [8]. It is used as a medicinal and edible plant by ethnic

groups such as Guan et al. and Sun et al. [9, 10] in China. It is a perennial woody vine of *Ficus* genus in the *Moraceae* family. The whole plant of *F. tikoua* Bur. is used as a traditional folk medicine to treat sore throat, cough, diarrhea, jaundice, rheumatism, edema, and dyspepsia [11–13]. In recent years, *F. tikoua* Bur. is gaining more and more attention as studies have shown that its extract has hypoglycemic [9], antibacterial [14], and antioxidant potential [14–16].

As research into plant-derived phytochemicals is increasing, regional medicinal plants from developing countries must also be promoted for the conservation of ecology and traditional medicinal knowledge and for providing medicine at low cost. With this background, herein, we have organized and summarized chemically diverse natural compounds isolated from *F. tikoua* Bur. and main experimental findings on their biological effects. This review will be helpful in underlining the emerging importance of the ethnomedicinal plant *F. tikoua* Bur. in medicine and the chemistry of plant-derived natural compounds.

2. Chemical Constituents

F. tikoua Bur. is rich in many secondary metabolites belonging to different phytochemical classes, including flavonoids, phenolic acids, terpenoids, steroids, coumarins, chromones, alkaloids, and hydrocarbons.

2.1. Flavonoids and Lignans. Approximately 57 flavonoid and lignan compounds (Figure 1; Table 1) including 21 isoflavones, 10 flavanones, 7 flavones, 7 flavanonols, 4 flavanols, 4 proanthocyanidins, 3 flavonol glycosides, and 1 isoflavanones have been identified from *F. tikoua* Bur. to date. Zhou et al. [17] in 2022 reported the isolation of twenty-two flavonoids including flavanones, isoflavones, and flavones from the petroleum ether and ethyl acetate portions of the 95% ethanol extract of *F. tikoua* Bur. aerial parts. Fu et al. [16] isolated a new isoflavonoid, ficusin C, from the rhizomes of *F. tikoua* Bur. Wei et al. [18] obtained seven flavonoid compounds (genistein, myrsininone A, wighteone or erythrinin B, lupiwighteone, naringenin, 6-prenylnaringenin, and 8-prenylnaringenin) from the *F. tikoua* Bur. stem for the first time. There are only few reports of extraction of flavanols and flavonols from *F. tikoua* Bur. Wei's group [19] isolated catechin and quercetin-catechin dimer from the water-soluble portion of the methanol extract of *F. tikoua* Bur. stems. In the same paper, the authors also isolated three proanthocyanidins: arecatannin, procyanidin B, and (epi)afzelechin-(epi)catechin. Yang's group [20] and Fu's group [16] reported the isolation of flavonol quercetin from *F. tikoua* Bur. Zhou et al. [21] in 2018 reported the isolation of a new isoflavone (ficustikounone A) and 22 other flavonoids (flavone, flavanone, isoprenylated flavanone, and isoflavones) from *F. tikoua* Bur. He et al. [22] used aerial parts of *F. tikoua* Bur. to extract lignans and neolignans, such as ssioriside and (+)-isolariciresinol, (−)-isolariciresinol-9-O-β-D-glucopyranoside. Yang's group [23] investigated the flavonoid content in different parts of *F. tikoua* Bur.: old leaves, young leaves, and stems. The authors found the highest content of flavonoids in the old leaves of the plant (147.5 mg/g), whereas the flavonoid contents in young leaves and stems of the plant were 107.67 mg/g and 91.69 mg/g, respectively.

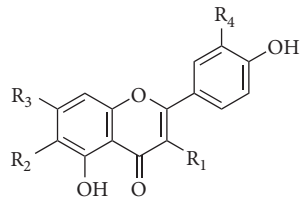
2.2. Phenolic Acids and Phenolic Glycosides. Phenolic acids and their derivatives (esters, aldehydes, and glycosides) have also been reported in the extract of *F. tikoua* Bur. (Figure 2; Table 2). Jiang et al. [24] isolated ten phenolic glycosides from the ethanol extract of *F. tikoua*; among these ten phenolic glycosides, four were isolated for the first time (Table 2). The other examples of phenolic acids and their derivatives isolated from *F. tikoua* Bur. are as follows: caffeic acid methyl ester [9], o-hydroxybenzoic acid or salicylic acid [25], 3,4-dihydroxybenzoic acid or protocatechuic acid [25, 26], p-hydroxybenzoic acid [26], vanillic acid [27], 3,4-dihydroxybenzaldehyde [26], and protocatechuic acid methyl ester [26].

2.3. Terpenes or Terpenoids. Phytochemical investigation on *F. tikoua* Bur. by many research groups has also yielded terpene compounds (Figure 3; Table 3) [20, 24, 27]. Terpenes are also called isoprenoids because they contain five-carbon isoprene units or molecules (CH_2=C(CH3)CH=CH2) as a building block in their structures. On the basis of the number of isoprene units, terpenes can be classified into following groups: (i) monoterpenes (2 isoprene units), (ii) sesquiterpenes (3 isoprene units), (iii) diterpenes (4 isoprene units), (iv) triterpenes (6 isoprene units), and (v) tetraterpenes (8 isoprene units). Terpenes of all classes except tetraterpenes have been isolated from *F. tikoua* Bur.

Very recently, Tian et al. [28] identified many terpene compounds in the essential oil of *F. tikoua* Bur. Sesquiterpenes containing different skeletons such as eudesmane (e.g., β-selinene), cadinane (e.g., α-cadinol), cedrane (e.g., α-cedrol), farnesane (e.g., d-nerolidol), and aromadendrane (e.g., spathulenol) have been identified in *F. tikoua* Bur.

2.4. Steroids. Steroids are another important class of chemical compounds that have been isolated from *F. tikoua* Bur. (Figure 4; Table 4). These include 5α-stigmastane-3,6-dione, β-sitosterol, ergosterol, stigmastane-3β,5α,6β-triol, stigmasta-3,5-dien-7-one, stigmast-4-en-3-one, β-stigmasterol, simiarenol, and 3β-hydroxystigmast-5-en-7-one [9, 20, 26, 29–31]. Guan's group [9] have also reported the isolation of a steroidal glycoside named daucosterol from *F. tikoua* Bur,

2.5. Other Compounds. Chemical compounds belonging to chemical classes other than previously mentioned have also been reported from *F. tikoua* Bur. by multiple studies (Figure 5; Table 5). Wei et al. [15] isolated two benzofuran glycosides, 6-carboxyethyl-7-methoxyl-5-hydroxy-benzofuran 5-O-β-D-glucopyranoside and 6-carboxyethyl-5-hydroxybenzofuran 5-O-β-D-glucopyranoside, from the extract of *F. tikoua* Bur. stems. Similarly, another benzofuran glycoside, 6-(2-carboxyvinyl)-7-methoxy-5-hydroxybenzofuran-5-O-β-D-glucopyranoside, was obtained by Wei



1 $R_1 = H; R_2 = H; R_3 = OH; R_4 = H$

2 $R_1 = OH; R_2 = H; R_3 = OH; R_4 = OH$

3 $R_1 = H; R_2 = H; R_3 = OH; R_4 = OH$

4 R_1 = rutinose; $R_2 = H; R_3 = OH; R_4 = H$

5 R_1 = rutinose; $R_2 = H; R_3 = OH; R_4 = OH$

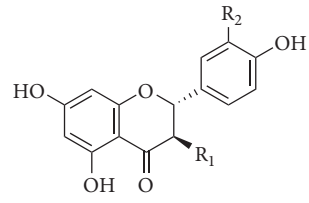
6 $R_1 = H; R_2 = H; R_3 = OCH_3; R_4 = H$

7 $R_1 = OH; R_2 = H; R_3 = OH_3; R_4 = H$

8 $R_1 = H; R_2$ = OGlc; $R_3 = OH; R_4 = H$

9 $R_1 = H; R_2$ = Glc; $R_3 = OH; R_4 = H$

10 R_1 = OGlc; $R_2 = H; R_3 = OH; R_4 = OH$

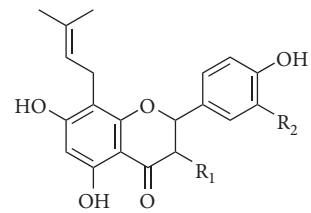


11 $R_1 = OH; R_2 = H; R_3 = OH$

12 $R_1 = OH; R_2 = H; R_3 = H$

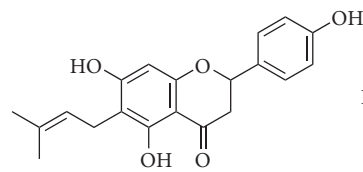
13 $R_1 = H; R_2 = OH; R_3 = H$

14 $R_1 = OH; R_2 = OH; R_3 = H$

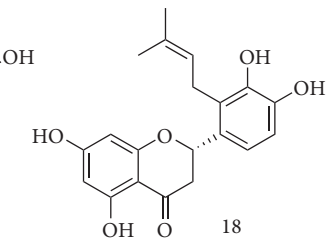


15 $R_1 = H; R_2 = OH$

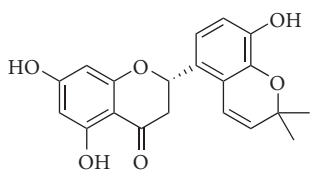
16 $R_1 = OH; R_2 = H$



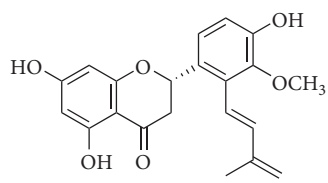
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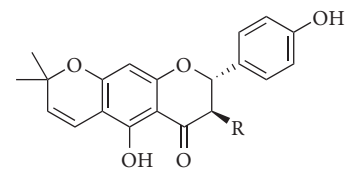
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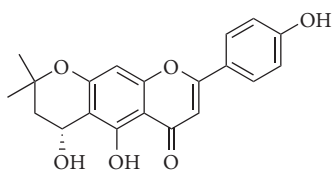


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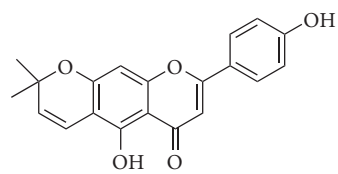


21 R = H

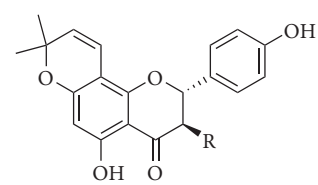
22 R = OH



23

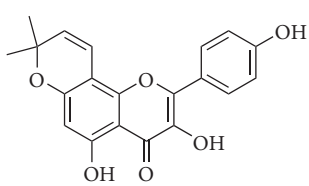


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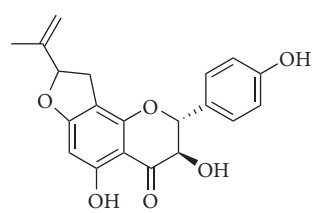


25 R = H

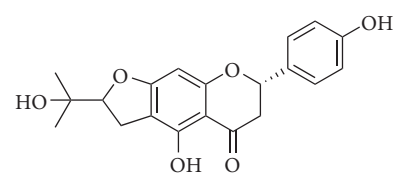
26 R = OH



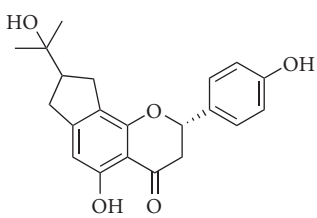
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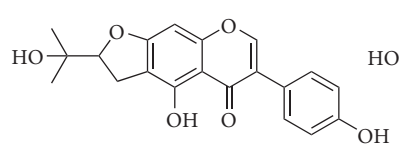
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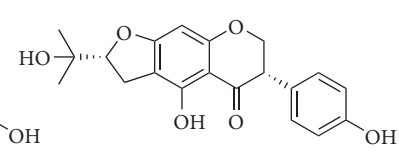
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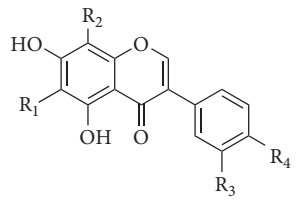
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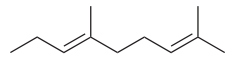


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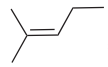
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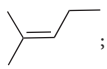
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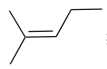


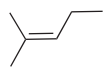
33 $R_1 = H$; $R_2 = H$; $R_3 =$  ; $R_4 = OH$

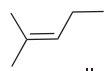
34 $R_1 = H$; $R_2 = H$; $R_3 = H$; $R_4 = OH$

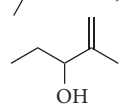
35 $R_1 = H$; $R_2 = H$; $R_3 =$  ; $R_4 = CH_3$

36 $R_1 =$  ; $R_2 = H$; $R_3 = H$; $R_4 = OH$

37 $R_1 = H$; $R_2 =$  ; $R_2 = H$; $R_4 = OH$

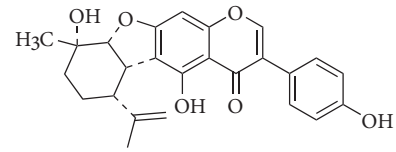
38 $R_1 = H$; $R_2 = H$; $R_3 =$  ; $R_4 = OH$

39 $R_1 = H$; $R_2 = H$; $R_3 =$  ; $R_4 = H$

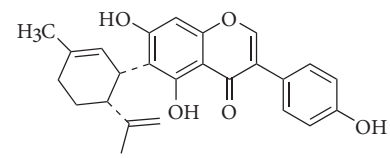
40 $R_1 = H$; $R_2 = H$; $R_3 =$  ; $R_4 = CH_3$

41 $R_1 = H$; $R_2 = H$; $R_3 = H$; $R_4 = OCH_3$

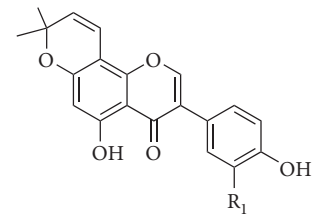
42 $R_1 = H$; $R_2 = H$; $R_3 = H$; $R_4 = OGlc$



43



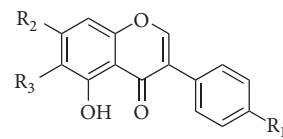
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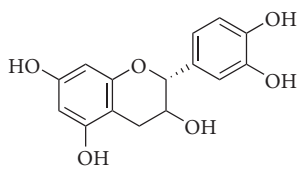
45 $R_1 = OH$; $R_2 = CH_3$

46 $R_1 = H$; $R_2 = CH_3$

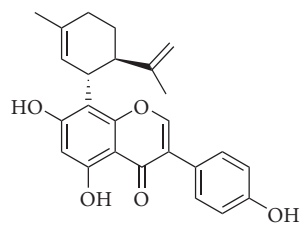
47 $R_1 = OH$; $R_2 = CH_3OH$



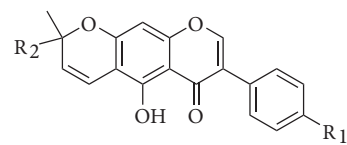
48 $R_1 = OH$; $R_2 = OGlc$: $R_3 = OH$



49



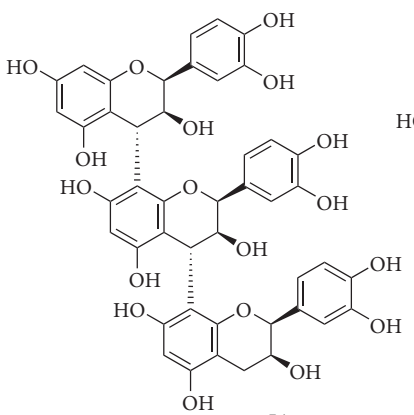
50



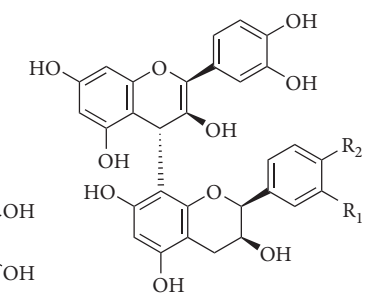
51 $R_1 = OH$; $R_2 = CH_3$

52 $R_1 = OCH_3$; $R_2 = CH_3$

53 $R_1 = OH$; $R_2 = CH_2OH$

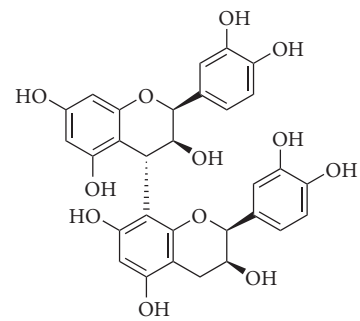


54



55 $R_1 = OH$; $R_2 = OH$

56 $R_1 = H$; $R_2 = OH$



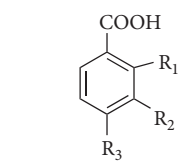
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(b)

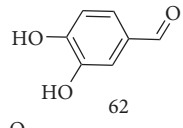
Figure 1: Structures of the flavonoids and lignans found in *F. tikoua* Bur.

Table 1: Flavonoids and lignans isolated from *F. tikoua* Bur.

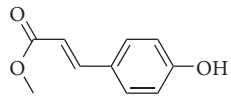
No.	Compound names	Flavonoid class	References
1	Apigenin	Flavone	[14, 20, 26]
2	Quercetin	Flavonol	[14, 16]
3	Luteolin	Flavone	[14]
4	Nicotiflorin	Flavonol glycoside	[19]
5	Rutin	Flavonol glycoside	[19]
6	7-O-methylapigenin	Flavone	[21]
7	Kaempferol	Flavonol	[17]
8	Astragalin	Flavone	[17]
9	Isovitexin	Flavone	[17]
10	Quercetin-3-O-β-D-glucopyranoside	Flavonol glycoside	[17]
11	(2R, 3R)-(+)-dihydroquercetin	Flavanonol	[14]
12	Aromadendrin	Flavanonol	[17]
13	Eriodictyol	Flavanone	[14, 17, 18]
14	Naringenin	Flavanonol	[14, 17]
15	8-Prenylnaringenin	Flavanone	[18, 20]
16	Neophellamuretin	Flavanonol	[21]
17	6-prenylnaringenin	Flavanone	[18]
18	(S)-5,7,3,4-tetrahydroxy-2-(3-methylbut-2-enyl)flavanone	Flavanone	[32]
19	Ficustikousins A	Flavanone	[32]
20	Ficustikousins B	Flavanone	[21, 32]
21	(S)-paratocarpin K	Flavanone	[32]
22	Afzelin A	Flavanonol	[17]
23	(1″R)-5,4′,1″-trihydroxy-6,7-(3″,3″-dimethylchroman) flavone	Flavone	[21]
24	Carpachromene	Flavone	[17, 21]
25	Citflavanone	Flavanone	[17, 21]
26	Yukovanol	Flavanonol	[17]
27	Citrusinol	Flavonol	[17]
28	Phellodensin A	Flavanonol	[17]
29	AF-6PN-3	Flavanone	[21]
30	Phellodensin D	Flavanone	[21]
31	Erythrinin C	Isoflavone	[21]
32	Ficustikounone A	Isoflavanone	[21]
33	Myrsininone A	Isoflavone	[18, 21]
34	Genistein	Isoflavone	[18, 21, 26]
35	3′-(3-Methylbut-2-enyl)biochanin A	Isoflavone	[21, 32]
36	Wighteone	Isoflavone	[17, 18, 21, 37]
37	Lupiwighteone	Isoflavone	[18, 37]
38	Isowigtheone	Isoflavone	[21]
39	Vogelin E	Isoflavone	[21]
40	Schliebenone A	Isoflavone	[21]
41	Prunetin	Isoflavone	[17]
42	Genistein-4-O-β-D-glucopyranoside	Isoflavone	[17]
43	Ficusin C	Isoflavone	[16]
44	6-[(1R*, 6R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5,7,4′-trihydroxyisoflavone	Isoflavone	[17]
45	5,3′,4′-trihydroxy-2″,2″-dimethylpyrano (5″, 6″ : 7, 8) isoflavone	Isoflavone	[18]
46	Derrone	Isoflavone	[17]
47	Hydroxyderrone	Isoflavone	[21]
48	Genistein 7-O-β-D-glucopyranoside	Isoflavone	[17]
49	Catechin	Flavonol	[19, 22]
50	Ficusin A	Isoflavone	[16, 17]
51	Alpinumisoflavone	Isoflavone	[16, 17]
52	4′-O-methyl-alpinumisoflavone	Isoflavone	[16]
53	Hydroxyalpinumisoflavone	Isoflavone	[27]
54	Arecatannin	Proanthocyanidin	[19]
55	Quercetin-catechin	Proanthocyanidin	[19]
56	(epi)afzelechin-(epi)catechin	Proanthocyanidin	[19]
57	Procyanidin B	Proanthocyanidin	[19]



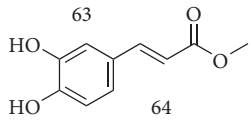
58 R_1 = OH; R_2 = H; R_3 = H
59 R_1 = H; R_2 = H; R_3 = OH
60 R_1 = H; R_2 = OH; R_3 = OH
61 R_1 = H; R_2 = OCH_3; R_3 = OH



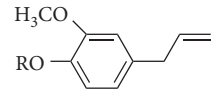
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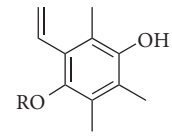
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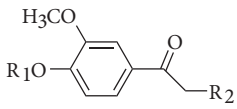
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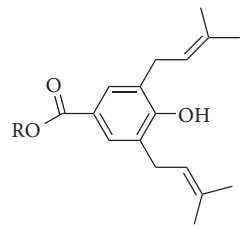
65 R = β-D-api-(1 → 6)-β-D-glc



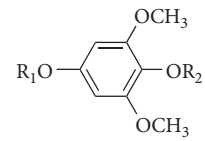
66 R = β-D-xyl-(1 → 6)-β-D-glc



67 R_1 = β-D-api-(1 → 2)-β-D-glc; R_2 = CH_3
68 R_1 = β-D-glc-R_2 = CH_2OH
69 R_1 = β-D-api-(1 → 6)-β-D-glc; R_2 = CH_3
70 R_1 = β-D-glc-R_2 = CH_3



71 R = β-D-glc



72 R_1 = β-D-api-(1 → 2)-β-D-glc; R_2 = CH_3
73 R_1 = β-D-glc-R_2 = CH_3
74 R_1 = β-D-glc-R_2 = H

Figure 2: Structures of the phenolic acids and their derivatives found in *F. tikoua* Bur.

Table 2: Phenolic glycosides isolated from *F. tikoua* Bur.

No.	Compound names	Reference
58	Salicylic acid	[25]
59	Protocatechuic acid methyl ester	[26]
60	p-Hydroxybenzoic acid	[26]
61	Vanillic acid	[24]
62	3,4-Dihydroxybenzaldehyde	[26]
63	Methyl p-coumarate	[9]
64	Caffeic acid methyl ester	[9]
65	2-Methoxy-4-allylphenyl-1-O-β-D-apiofuranosyl-(1⟶6)-β-D-glucopyranoside	[24]
66	2-Ethylene-3,5,6-trimethyl-4-phenol-1-O-β-D-xylopyranosyl-(1⟶6)-β-D-glucopyranoside	[24]
67	3-Methoxy-4-O-β-D-apiofuranosyl-(1⟶2)-β-D-glucopyranosylpropiophenone	[24]
68	3-Hydroxy-1-(4-O-β-D-glucopyranosyl-3-methoxyphenyl) propan-1-one	[24]
69	3-Methoxy-4-O-β-D-apiofurano-syl-(1⟶6)-β-D-glucopyranosylpropiophenone	[24]
70	Baihuaqianhuoside	[24]
71	4-Hydroxy-3,5-bis(30-methyl-2-butenyl)benzoic acid-O-β-D-glucopyranoside	[24]
72	3,4,5-Trimethoxyphenol-1-O-β-D-apiofuranosyl-(1⟶6)-β-D-glucopyranoside	[24]
73	3,4,5-Trimethoxyphenol-1-O-β-D-glucopyranoside	[24]
74	3,5-Dimethoxy-4-hydroxybenzoicacid-O-β-D-glucopyranoside	[24]

et al. [19] from the water-soluble portion of the methanol extract of *F. tikoua* Bur. stems.

Coumarins and chromones are oxygenated heterocyclic compounds that belong to the benzopyrone chemical class. Bergapten is the most common coumarin that has been isolated from *F. tikoua* Bur. by more than one study [9, 22, 29, 30, 32]. Esculetin isolated by Zhou et al. [26] and nodakenin and psoralen isolated by He et al. [22] are other examples of coumarins presented in *F. tikoua*. Very recently, Zhou's group [17, 26] reported isolation of one new and three chromone compounds from the aerial parts of *F. tikoua*: (±)-ficunomone, 5,7-dihydroxychromone, noreugenin, and alloptaeroxylin. They also reported the extraction of two alkaloids, neoechinulin A and indole-3-carboxylic acid, for the first time from *F. tikoua* Bur.

Yang's group [33] in 2016 investigated the *F. tikoua* Bur. fruit for the identification of volatile compounds. The authors detected the presence of 152 chemical compounds in *F. tikoua* Bur. fruits. Among these, esters, alcohols, and alkenes were prominent aroma components class accounting for 33.06%, 13.14%, and 13.18%, respectively, of the total aroma component detected in the *F. tikoua* Bur. fruits. The major aroma compounds found in the study were as follows: guaiacol, cyclobutane carboxylic acid dodecyl ester, *n*-tridecane, 2-tridecanone, cyclohexasiloxane, cyclobutanecarboxylic acid decyl ester, methyl nonyl ketone, and acetic acid.

Many fatty acids (saturated and unsaturated both), fatty acid methyl esters, fatty acid ethyl esters, fatty acid butyl esters, fatty acid isopropyl esters, and fatty aldehydes have been reported from *F. tikoua* Bur. extracts [28, 34].

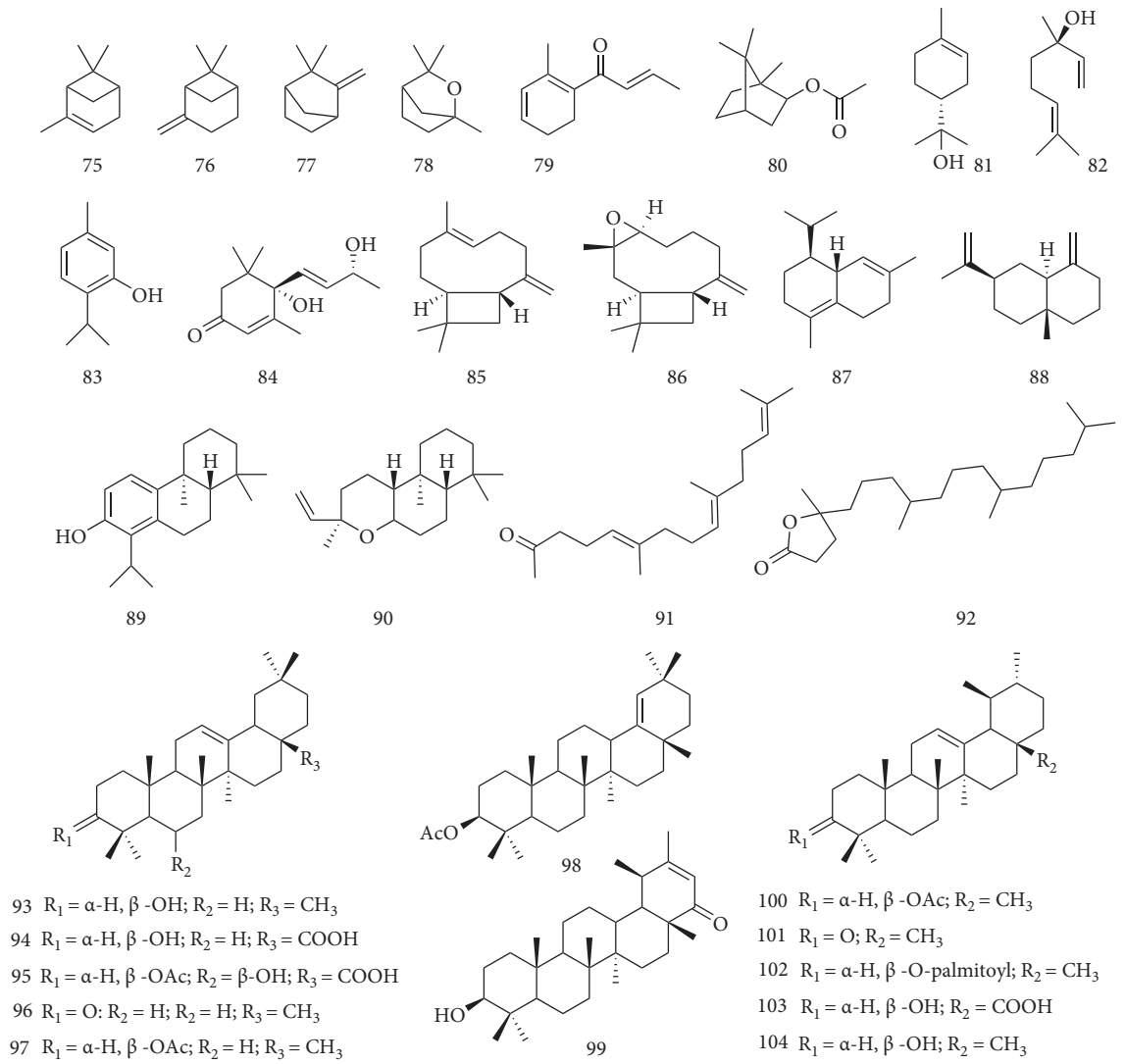


Figure 3: Structures of the terpenes and terpenoids found in *F. tikoua* Bur.

Additionally, benzoquinone [27], imidazole [9], alpha-tocopherol [34], naphthalene [22], and numerous hydrocarbons (alkanes, alkenes, and styrene) have also been identified in *F. tikoua* Bur. Tian's group [28] identified fifty-three compounds in the essential oil of *F. tikoua* Bur. by GC-FID/MS, and among the identified components, palmitic acid (51.13%) and linoleic acid (47.54%) were the major fraction.

3. Biological Activities of *F. tikoua* Bureau

Crude extract of *F. tikoua* Bur. and natural compounds isolated from it have been found to possess antioxidant, antibacterial, anti-inflammatory, antiviral, and antitumor activities.

3.1. Antimicrobial Effect. Xiang and Wang [35] used the agar plate diffusion method to quantitatively detect the antibacterial effect of *F. tikoua* Bur. water extract on gram-negative bacteria, *Escherichia coli* and *Shigella dysenteriae*, and gram-positive bacteria, *Staphylococcus aureus*. The results showed that *F. tikoua* Bur. water extract had a concentration-dependent antibacterial effect on *Shigella dysenteriae* and *Staphylococcus aureus* but had no effect on *Escherichia coli*. Wang et al. [36] used the conventional agar diffusion method to perform *in vitro* antibacterial tests of *F. tikoua* Bur. extract on *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Pseudomonas aeruginosa,* and clinically isolated methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The results showed that the extract had no obvious inhibitory effects on *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Pseudomonas aeruginosa* but had inhibitory effects on the four strains of clinically isolated MRSA. Yang et al. [14] determined the antibacterial activity of ethanol extract from *F. tikoua* Bur. roots by using the paper disc diffusion method. The authors found that 95% ethanol extract of *F. tikoua* Bur. roots had clear but weak inhibitory effects on five different bacteria, with the order of inhibition was as follows: *Shigella flexneri* > *Bacillus megaterium* > *Proteus* sp. > *Pseudomonas aeruginosa* > *Micrococcus luteus*.

Table 3: Terpenes isolated from *F. tikoua* Bur.

No.	Terpene compounds	Terpene class	Reference
75	α-Pinene	Monoterpene	[28]
76	β-Pinene	Monoterpene	[28]
77	Camphene	Monoterpene	[28]
78	1,8-Cineole	Monoterpene	[28]
79	β-Damascenone	Monoterpene	[28]
80	1-Bornyl acetate	Monoterpene	[28]
81	α-Terpineol	Monoterpene	[28]
82	Linalool	Monoterpene	[28]
83	Thymol	Monoterpene	[28]
84	Bluemenol A	Sesquiterpene	[28]
85	β-Caryophyllene	Sesquiterpene	[28]
86	Caryophyllene oxide	Sesquiterpene	[28]
87	δ-Cadinene	Sesquiterpene	[28]
88	β-Selinene	Sesquiterpene	[28]
89	Totarol	Diterpene	[28]
90	3,4a,7,7,10a-pentamethyl-3-vinyl-dodecahydro-1H-benzo[f]chromene	Diterpene	[34]
91	Farnesyl acetone	Diterpene	[28]
92	4,8,12,16-Tetramethylheptadecan-4-olide	Diterpene	[28]
93	β-Sitosterol	Triterpene	[14, 26, 27, 29]
94	Oleanolic acid	Triterpene	[9, 14, 29]
95	3-O-acetyloleanolic acid	Triterpene	[14]
96	β-Amyrenone	Triterpene	[30]
97	β-Amyrin acetate	Triterpene	[30]
98	Germanicol acetate	Triterpene	[30]
99	22-Oxo-20-taraxasten-3β-ol	Triterpene	[26]
100	α-Amyrin acetate	Triterpene	[25, 30]
101	α-Myrenone	Triterpene	[25, 30]
102	β-Amyrin palmitate	Triterpene	[30]
103	Ursolic acid	Triterpene	[30]
104	α-Amyrin	Triterpene	[29]

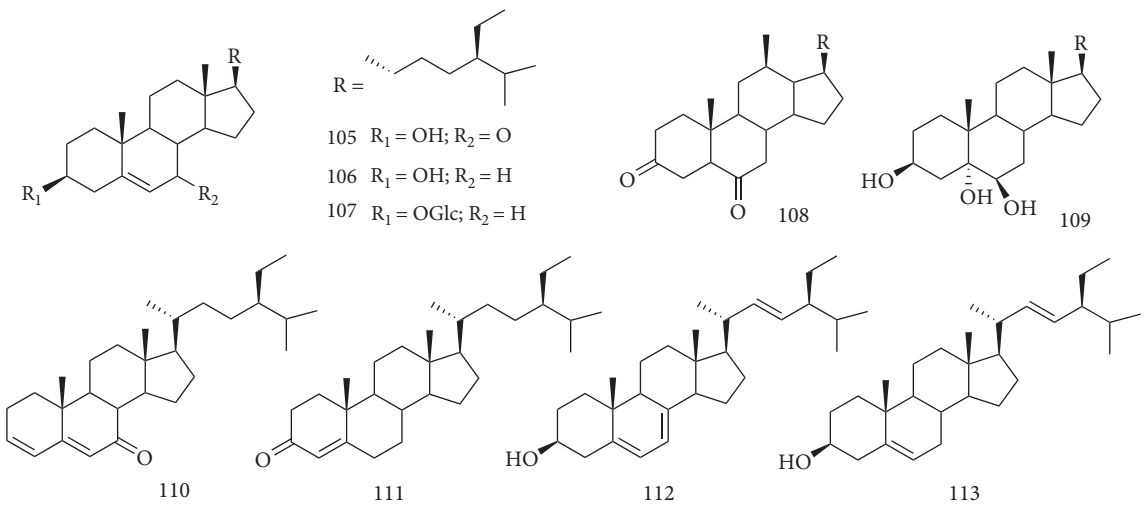


Figure 4: Structures of the steroids found in *F. tikoua* Bur.

Wei et al. [18] conducted *in vitro* antifungal tests against *Phytophthora infestans* via spore germination assay for the compounds isolated from *F. tikoua* Bur: genistein, myrsininone *A*, wighteone, lupiwighteone, naringenin, and 8-prenylnaringenin. All isolated compounds except myrsininone *A* showed antifungal activity. The strongest antifungal activity against *Phytophthora infestans* was registered for naringenin, 8-prenylnaringenin, and 6-prenylnaringenin, with IC_{50} values of 10.447, 10.864, and 16.828 μg/mL, respectively [18]. In an another study, Wei et al. [37] isolated a new pyrano-isoflavone (5,3′,4′-trihydroxy-2″,2″-dimethylpyrano (5″, 6″ : 7, 8) isoflavone) from *F. tikoua* Bur. stems and reported that the compound possesses antifungal activity against *Phytophthora infestans* with an IC_{50} value of 262.442 μg/mL.

Du [38] conducted *in vitro* antibacterial experiments on the water extract of *F. tikoua* Bur. against *Staphylococcus*

Table 4: Steroids isolated from *F. tikoua* Bur.

No.	Compound names	Reference
105	3β-Hydroxystigmast-5-en-7-one	[20]
106	β-Sitosterol	[9, 20, 27]
107	Daucosterol	[9]
108	5α-Stigmastane-3,6-dione	[20]
109	Stigmastane-3β,5α,6β-triol	[30]
110	Stigmasta-3,5-dien-7-one	[31]
111	Stigmast-4-en-3-one	[9, 31]
112	Ergosterol	[31]
113	β-Stigmasterol	[20, 27]

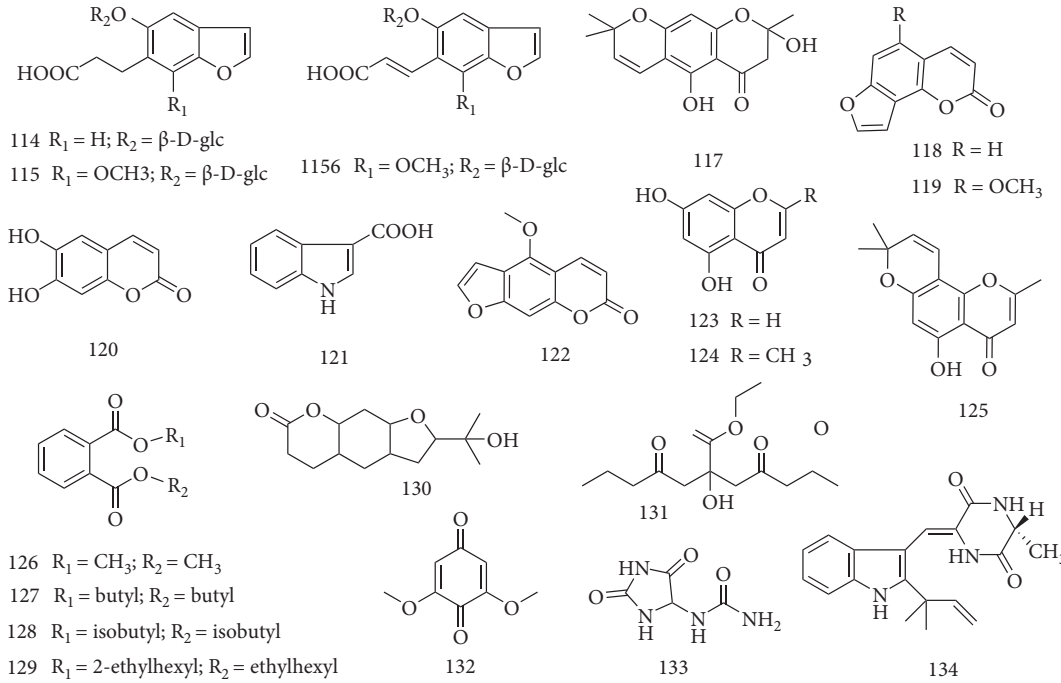


Figure 5: Structures of some of other compounds found in *F. tikoua* Bur.

aureus, *Staphylococcus epidermidis*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus* sp., and *Pseudomonas aeruginosa* via Oxford cup method and agar dilution method. The *F. tikoua* Bur. extracts showed antibacterial activity against all tested bacteria except *Escherichia coli*. In the study of Tian et al. [28], the essential oil from *F. tikoua* Bur. revealed significant antibacterial activity in a microdilution assay against *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*. The values of zone of inhibition, minimal inhibitory concentration (MIC), and minimal bactericidal concentration (MBC) of essentials oils in the study were ranged from 7.89 to 10.59 mm, 0.20 to 6.25 mg/mL, and 0.20 to 12.50 mg/mL, respectively. Cheng et al. [39] studied the antibacterial effects of three different solvent extracts of *F. tikoua*: petroleum ether, ethyl acetate, and n-butanol. All three *F. tikoua* Bur. crude extracts exhibited antibacterial activities against *Escherichia coli*, *Staphylococcus epidermidis*, *Shigella*, and *Staphylococcus aureus*.

Although none of these studies undertook mechanistic study of the antimicrobial effects shown by *F. tikoua* Bur. extracts and compounds isolated from it, as per existing literature plant extracts decrease cytoplasmic pH of bacterial cells and hyperpolarize the bacterial cell membrane, thus resulting in the disruption of cell wall, leakage of cytoplasmic contents, and ultimately the death of bacterial cells [40, 41]. Similarly, isoflavone biochanin A has previously been found to exert its antibacterial activities against MRSA, *Chlamydia* spp., and *Mycobacterium* strains by inhibiting their efflux pumps system [41]. Although the antibacterial activity of 3′-(3-methylbut-2-enyl)biochanin *A*, a biochanin A derivative isoflavone, isolated from *F. tikoua* Bur. was not studied by Wu et al. [32] and Zhou et al. [21], it is possible that this compound also has similar antibacterial activity and mechanism as that of biochanin *A*.

3.2. Antitumor Effect. Plant phenolic compounds show antitumor effects, which can be attributed to the presence of aromatic rings and hydroxyl groups in their structure. Presence of more than one hydroxyl group and short fatty acid side chain in certain plant phenolic compounds makes

Table 5: Other compounds found in *F. tikoua* Bur.

No.	Compound names	Reference
114	6-Carboxyethyl-5-hydroxybenzofuran	[15]
115	5-O-β-D-glucopyranoside, 6-carboxyethyl-7-methoxyl-5-hydroxy-benzofuran 5-O-β-D-glucopyranoside	[15]
116	6-(2-Carboxyvinyl)-7-methoxy-5-hydroxy-benzofuran	[19]
117	5-O-β-D-glucopyranoside (±)-ficunomone	[17]
118	Angelicin	[31]
119	Isobergapten	[31]
120	Esculetin	[26]
121	Indole-3-carboxylic acid	[26]
122	Bergapten	[9, 22, 29, 30, 32]
123	5,7-Dihydroxychromone	[26]
124	Noreugenin	[26]
125	Alloptaeroxylin	[26]
126	Dimethyl phthalate	[31]
127	Dibutyl phthalate	[31]
128	Diisobutyl phthalate	[31]
129	Dihexyl phthalate	[31]
130	Marmesin	[31]
131	Triethyl citrate	[31]
132	2,6-Dimethoxy-1,4-benzoquinone	[27]
133	Allantoin	[9]
134	Neoechinulin A	[26]

them more potent than phenolic compounds with only one hydroxyl group [42]. *F. tikoua* Bur. extracts have been shown to have cytotoxic properties against tumor cells; for example, in the study of Tian et al. [28], the essential oil from *F. tikoua* Bur. exhibited significant cytotoxicity against A549, NCI-H1299, PC-3, and K562 tumor cells, with IC_{50} values of 131.08, 50.32, 120.58, and 31.68 μg/mL, respectively. The essential oil exhibited selective cytotoxicity to human tumor cell lines, with a significantly lower cytotoxicity to human normal cells MRC-5 ($IC_{50} = 161.75\,\mu$g/mL) than to tumor cells. Although, in literature, both fatty acids [42, 43] and terpenoids [44] have been shown to have antitumor activities, there is a possibility that majority of antitumor effect in the study of Tian et al. [28] could be due to palmitic acid and linoleic acid alone, but not from terpene compounds. The reason for it is that, in the essential oil extracted from *F. tikoua* Bur., major portion was of palmitic acid (51.13%) and linoleic acid (47.54%), whereas terpenes were only a minuscule amount in the essential oil.

As mentioned previously, Jiang et al. [24] isolated ten phenolic glycosides (Table 2) from *F. tikoua* Bur. rhizomes. These phenolic glycosides were tested for their cytotoxic effects against HeLa, K562, HL60, and HepG2 cancer cell lines via MTT (3-(4,5-dimeth-ylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. All the phenolic glycosides showed a varying degree of antitumor effects against tested cancer cell lines. The IC_{50} values of phenolic glycosides against HeLa, K562, HL60, and HepG2 cells were ranged from 16.0 ± 3.2 to $79.2 \pm 9.7\,\mu$M, 16.3 ± 3.8 to $102.5 \pm 11.3\,\mu$M, 15.1 ± 5.4 to $89.8 \pm 9.1\,\mu$M, and 15.1 ± 6.3 to $132.4 \pm 10.8\,\mu$M, respectively.

Tian et al. [30] tested the antitumor activities of compounds (bergapten, oleanolic acid, palmitic acid, β-amyrin palmitate, ursolic acid, nonacosane, germanicol acetate, triacontane acid, linoleic acid, stigmastane-3β,5α,6β-triol) extracted from *F. tikoua* Bur. against PC-3, K562, and A549 cell lines. The results showed that, among all extracted compounds from *F. tikoua* Bur. in the study, ursolic acid, which is a pentacyclic triterpene, had the highest cytotoxic activity against K562 with an IC_{50} value of 1.69 μg/mL, which was stronger than the positive control cisplatin ($IC_{50} = 10.21\,\mu$g/mL). Ursolic acid has been widely studied for its anticancer property; and it has been reported that ursolic acid interacts with a number of signaling molecules in cell signaling pathways, and it checks cell proliferation and causes apoptosis of tumor cells [45].

3.3. Antioxidant Activities. *F. tikoua* Bur. is rich in many phytochemicals such as flavonoids, terpenes, and phenolic acids, and thus it is no surprise that many studies have found antioxidant properties in its extracts. Yang et al. [14] used the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method to determine the antioxidant activities of different solvent extracts (ethanol, ethyl acetate, and n-butanol extracts) of *F. tikoua* Bur. roots. All extracts showed concentration-dependent strong DPPH free radical scavenging ability. Wei et al. [15] isolated two benzofuran glucosides, 6-carboxyethyl-5-hydroxybenzofuran 5-O-β-D-glucopyranoside and 6-carboxyethyl-7-methoxyl-5-hydroxy-benzofuran 5-O-β-D-glucopyranoside, from *F. tikoua* Bur. and found antioxidant activities for both the compounds with IC_{50} values of 242.8 and 324.9 μg/mL, respectively. Fu's group [16] investigated the free radical scavenging activity of five isoflavones and one flavonol isolated from F. tikoua Bur. (ficusin C, 6-[(1R*, 6R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5,7,4′-trihydroxyisoflavone, ficusin A, alpinumisoflavone, 4′-O-methylalpinumisoflavone, and quercetin) and reported that the EC_{50} values of the six compounds were 49.3 ± 7.8, 43.3 ± 6.9, 42.4 ± 6.6, 54.8 ± 9.7, and 83.6 ± 12.5, 4.2 ± 0.5, respectively. As it is clearly seen by the EC_{50} values, among

all six flavonoids, flavonol quercetin showed the maximum antioxidant capability, more than any other isoflavones in the experiment. It is because the total number of hydroxyl groups is one of the important factors for the flavonoid to be a potent antioxidant [46], and among the six flavonoids, quercetin had the maximum number of hydroxyl groups.

Cheng et al. [39] studied the free radical scavenging activity of the three different solvent extracts of *F. tikoua* Bur. The authors found that all three extracts could scavenge DPPH, hydroxyl, and superoxide free radicals in a concentration-dependent manner. He's group [22] isolated total seventeen chemical compounds of different classes (isoflavones, flavanols, coumarin, lignan, and neolignan) from *F. tikoua* Bur. and examined their DPPH radical scavenging rate, total antioxidant capacity, and superoxide anion scavenging capacity. Among all 17 isolated compounds from *F. tikoua* Bur., the following compounds were found to have significant antioxidant activity: ssioriside, huazhongilexin, 6,7-dimethoxy-4-hydroxy-1-naphthoic acid, ethy-3,4-dihydroxybenzoate, and 3,3′,4,4′-tetrahydroxy diphenyl.

3.4. Anti-Inflammatory Effect. Li et al. [47] in the study on 24 Australian and Chinese plants for their anti-inflammatory properties found moderate inhibition of cyclooxygenase-1 (COX-1) by ethanol extracts from *F. tikoua* Bur. stem, thus confirming its use as a traditional medicine in China for many diseases such as arthritis, edema, infections, and snakebite. Similarly, to find the plants having potential anti-inflammatory activities, Liao et al. [48] investigated many traditional Chinese herbs species for their effect on nitric oxide (NO) production in a murine macrophage-like cell line, RAW 264.7, which was activated by lipopolysaccharide (LPS) and interferon-γ (IFN-γ). *F. tikoua* Bur. was also one of the plants that were tested in this study. Extract prepared from syconium of *F. tikoua* Bur. showed significant inhibition of NO production by activated macrophage with an IC_{50} value of 17.51 μg/mL. The results suggested possible anti-inflammatory effect of *F. tikoua*. Inhibition of nitric oxide production appears to be the standard mechanism for the anti-inflammatory effect shown by *F. tikoua* Bur. because other studies have also proposed similar mechanism (that is inhibition of NO production by LPS-induced RAW 264.7 macrophage cells) for other plant-derived and commercially sourced phenolic compounds like kaempferol and its glycosides [49, 50].

3.5. Antidiabetic Effect. *F. tikoua* Bur. has also been reported to have a potential role against diabetes [16, 32]. The latest research by Zhou et al. [17] found that seven flavonoids isolated from *F. tikoua* Bur. could inhibit *a*-glucosidase, among which 6-[(1R^*, 6R^*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]5,7,4′-trihydroxyisoflavone and ficusin A exhibited the highest inhibitory activity, with IC_{50} values at 5.12 ± 0.10 and 3.43 ± 0.15 μM, respectively. Wu's group [32] isolated nine compounds from *F. tikoua* Bur. and tested their inhibitory activities against protein tyrosine phosphatase 1B (PTP1B), which plays an important role in insulin signaling, thus investigating possible antidiabetic action of *F. tikoua* Bur. In the study, isoprenylated flavonoids were found to inhibit PTP1B ($IC_{50} = 11.16$–40.37 μM), whereas compounds without isoprenoid group, flavonoid genistein and coumarin bergapten, were inactive against PTP1B. This study supports the previous findings that the prenylation of flavonoids increases their inhibitory activity against PTP1B compared with the nonprenylated flavonoids [51, 52]. Similarly, Fu's group [16] found α-glucosidase inhibitory activity and thus antidiabetic potential for all flavonoid compounds isolated from *F. tikoua* Bur. in the study (ficusin C, 6-[(1R^*, 6R^*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5,7,4′-trihydroxyisoflavone, ficusin A, alpinumisoflavone, 4′-O-methylalpinumisoflavone, and quercetin) with IC_{50} values of 62.4 ± 6.9, 32.5 ± 6.7, 84.6 ± 7.8, 73.3 ± 12.9, 85.4 ± 11.5, and 31.2 ± 5.7 μM, respectively.

3.6. Other Biological Effects. We found only a single study on the antiviral effect of *F. tikoua*. Zhang et al. [53] used respiratory syncytial virus (RSV), herpes simplex virus (HSV-1), coxsackievirus (COX-B5), and enterovirus 71 (EV71) to study the *in vitro* antiviral activity of different solvent extracts of *F. tikoua*. The results showed that the ethyl acetate extract had weak antiviral effects on EV71 and HSV-1, whereas the water extract of *F. tikoua* Bur. exhibited significant antiviral effects against COX-B5 and RSV.

Xiong and Li [54] investigated the effect of the different *F. tikoua* Bur. extracts on the tyrosinase activity. The results showed that the extracts had strong activation effect on tyrosinase, and the activation effect did not change linearly with the increase of concentration. The ethyl acetate extract had different activation effects on tyrosinase, and the active components in the extract had noncompetitive activation and mixed activation effects on tyrosinase. The study showed the therapeutic potential of *F. tikoua* Bur. in the treatment of skin hypopigmentation.

4. Conclusion

The present review provides an overview of the previous and current research on chemical compounds isolated from *F. tikoua* Bur. and summarizes their biological activities. In summary, many natural compounds of varied chemical classes have been isolated from different parts of *F. tikoua* Bur. (stems, roots, whole plant, aerial parts, and syconium) and have been found in various *in vitro* experiments to possess antimicrobial (antibacterial and antifungal), antiviral, antioxidant, antidiabetic, antitumor, and anti-inflammatory properties. These studies not only confirm the traditional usage of *F. tikoua* but also elucidate its new applications. Despite this, as can be concluded from this review, there are only few studies on chemical constituents of *F. tikoua* Bur. and its biological effects. Additionally, the lack of mechanistic study on the biological effects of *F. tikoua* Bur. is another research area that demands attention because understanding the mechanism of biological effects of medicinal plant extracts is the first step in their utilization for therapeutic application. Further research on the phytochemical and pharmacological aspects of *F. tikoua* Bur. should be pursued. Moreover, the

biological activities of *F. tikoua* Bur. have been tested only in *in vitro* settings. Phytochemicals from *F. tikoua* Bur. further needs to be studied in *in vivo* conditions for their therapeutic potential so that this traditional medicine can be brought to the new horizon of modern medicine.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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