Review

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Ethnomedicinal Uses, Phytochemistry, and Pharmacological Activity of the *Irvingia* Species

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Review

Ethnomedicinal Uses, Phytochemistry, and Pharmacological Activity of the *Irvingia* Species

Branly-Natalien Nguena-Dongue [1,†], Boniface Pone Kamdem [1,2,*,†], Paul Keilah Lunga [1] and Fabrice Fekam Boyom [1]

[1] Antimicrobial and Biocontrol Agents Unit (AmBcAU), Laboratory for Phytobiochemistry and Medicinal Plants Studies, Department of Biochemistry, Faculty of Science, University of Yaoundé I, P.O. Box 812, Yaoundé-Cameroon; Email: fabrice.boyom@fulbrightmail.org (FFB), lungapaul@yahoo.ca (PKL), nguenadonguebranlynatalien@gmail.com (BNND)

[2] Department of Basic and Applied Fundamental Sciences, Higher Institute of Agriculture, Forestry, Water and Environment (HIAFWE), University of Ebolowa, P.O. Box 755, Ebolowa-Cameroon; Email: ponekamdemboniface@gmail.com

* Correspondence: ponekamdemboniface@gmail.com; Tel.: (+237 680 98 76 69; +237 657 52 57 18).

† These authors have contributed equally to this work.

Abstract: Plants belonging to the genus *Irvingia* are widespread across the African and Southeast Asian regions of the world. *Irvingia gabonensis*, *Irvingia malayana*, and *Irvingia grandifolia* are among the commonly used species in ethnomedicine, especially in Africa. Fever, scabies, toothache, inflammation, and liver and gastrointestinal disorders are among the pathological conditions that are reverted by *Irvingia* plants upon traditional preparations. Modern pharmacological investigations have substantiated the ethnomedicinal uses of *Irvingia* spp. Reports on the phytochemical analysis of *Irvingia* plants have revealed the presence of a number of secondary metabolites, such as flavonoids, phenolic compounds, tannins, saponins and alkaloids. Based on the foregoing, the present study provides a comprehensive evaluation of reports on the ethnomedicinal use, phytochemistry, pharmacology, and toxicity of plants from the genus *Irvingia*. Relevant information on *Irvingia* plants was mostly obtained from major scientific databases from their inception until July 2023. As a result, more than forty compounds have been identified in *Irvingia* spp. proving the abundance of secondary metabolites in these plants. Reports have pointed out modern pharmacological activities, such as antiprotozoal, antimicrobial, antioxidant, antidiabetic, anti-inflammatory, and hepatoprotective activities. The present study provides more insights for the successful utilization of *Irvingia* plants and may guide further research on their therapeutic potential in the treatment of various diseases.

Keywords: *Irvingia* spp.; ethnomedicinal uses; phytochemistry; pharmacological activity; toxicity.

1. Introduction

From the Irvingiaceae family, *Irvingia* (commonly called wild mango, bush mango, or ogbono) is a genus that is mainly found in African and Southeast Asian regions [1]. Taxonomically, the World Flora Online has published seven accepted species of *Irvingia*. These include *Irvingia malayana*, *Irvingia excelsa*, *Irvingia fusca*, *Irvingia gabonensis*, *Irvingia wombolu*, *Irvingia smithii*, and *Irvingia grandifolia* [2]. Also called bush mango or African mango, *Irvingia gabonensis* (bark) is used for the traditional treatment of dysentery, scabies, and toothache and skin diseases [3]. In combination with palm oil, the leaves of *I. gabonensis* are used to stop hemorrhage in pregnant women [4]. *Irvingia gabonensis* bark is very effective for treating skin bruises, toothaches, dysentery and hernia [3]. The hepatoprotective activity of *Irvingia gabonensis* was also reported by several authors [5, 6]. The bark decoction of *Irvingia grandifolia* is used to relieve pain and for bathing to treat fever in children [7]. Various parts of *Irvingia grandifolia* and *Irvingia malayana* are used to treat a number of diseases, such as diabetes, asthenia, icterus, dysentery, toothache, diarrhea, scabies, inflammation and yellow fever [8, 9, 10]. Modern pharmacological properties of *Irvingia* spp. revealed antidiarrheal [11], antimicrobial [12, 13, 14], cytotoxic [15], antioxidant and antidiabetic [16, 17] activities, among others. The phytochemical

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screening of *Irvingia* spp. revealed the presence of saponins, tannins, alkaloids, flavonoids, cardiac glycosides, steroids, carbohydrates, volatile oils and terpenoids [3], as well as phenolic acids, such as 2,3,8-tri-O-methylellagic acid [18]. Regarding phytochemistry and pharmacological studies on *Irvingia* spp., a number of information is available across the literature. However, few reviews have been reported on *Irvingia* plants. In fact, emphasis has been placed mostly on food application [19] and cardiovascular disease outcomes [20] of *Irvingia* species. Thus, comprehensive reviews and/or monographs on the application of *Irvingia* species as ethnomedicinal plants, are needed. In this line, the present work aims to summarize existing information regarding ethnomedicinal uses, phytochemistry and pharmacological activities of *Irvingia* plants.

2. Research methods

The present study aims to substantially review the traditional uses, phytochemistry, and pharmacological activity of *Irvinvia* plants.

2.1. Search of literature

Information related to the pharmacological activity of chemical constituents from *Irvingia* plants was obtained from published and unpublished materials across the literature. Relevant data were obtained from databases, such as PubMed (National Library of Medicine), American Chemical Society (ACS), Science Direct, SciFinder, Web of Science, Scopus, Wiley, Google Scholar, and Springer, from their respective inception until August 2023. Furthermore, theses, dissertations, and textbooks were searched to obtain the relevant data. The search terms included "*Irvingia*"; OR "*Irvingia* spp." AND "Traditional uses"; "*Irvingia*"; OR "*Irvingia* spp." AND "Phytochemistry"; "*Irvingia*" OR "*Irvingia* spp." AND "Pharmacology"; "*Irvingia*" OR "*Irvingia* spp." AND "Pharmacological activity"; and "*Irvinbgia*" OR "*Irvingia* spp." AND "Toxicity". In addition, books, scientific reports, dissertations, theses and articles published in peer-reviewed journals were also scrutinized and searched. References obtained from various searches were also examined to obtain further additional information.

2.2. Data extraction and synthesis

Data extraction and synthesis were conducted by the first and second authors and confirmed by the other authors. Figures or tables were used to gather appropriate data that were further summarized and analyzed. In addition, a descriptive narration was used to provide a summary of the results. The chemical structures of pharmacologically active compounds are provided using graphical representations.

2.3. Results of the literature search

A total of 1842 ("*Irvingia*": 805; "*Irvingia* and traditional uses": 345; *Irvingia* and Phytochemistry": 45; *Irvingia* and Pharmacological activity": 193; "*Irvingia* and Pharmacology": 182; "*Irvingia* and Toxicity": 272) significant records were obtained, of which 1802 were disqualified and excluded after screening the titles or abstracts. Forty full-length research articles were exploited to collect relevant information. In addition, important facts obtained from unpublished materials were also included.

3. Traditional uses

The genus *Irvingia* encompasses seven species, among which six occur in tropical Africa and one in Southeast Asia. These are *Irvingia gabonensis*, *I. excels*, I. *wombolu*, *I. orbor*, *I. smithil* and *I. midbr*. However, two common species of the tree, *I. gabonensis* have a sweet edible pulp, while *I. wombulu* has a bitter edible pulp, although both are fit for human consumption and used as such in Africa [3] and form part of the traditional diets of several people, especially in rural areas. Other common *Irvingia* species include *Irvingia tenuinucleata* and *Irvingia grandifolia*, among others. *Irvingia gabonensis* seeds are prominent in international trade in West Africa. The major destinations of the products are Nigeria, Gabon, Liberia, and Sierra Leone, while the humid lowland countries of Cameroon, Nigeria,

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and Côte d'Ivoire are the main sources of the products [3]. These plant species are used in traditional medicine to treat a number of disease conditions, including diarrhea, scabies, toothache, yellow fever, inflammation, and liver and gastrointestinal disorders (Table 1) [21].

In Cameroon, the decoction of *I. gabonensis* and *I. wombolu* seeds is administered twice a day until body weight is reduced [8, 22]. In Gabon, the bark decoction of *I. grandifolia* (common name: Mulenda) is used in a bath to treat asthenia; however, in children, the leaves are pounded and mixed with food to overcome this disease condition [23]. Commonly called Aslotin in Benin, *Irvingia gabonensis* is used to treat icterus [24]. In Nigeria, *Irvingia tenuinucleata* is also called Bush mango or Oro, and its fruits and bark have been used traditionally to treat diarrhea, scabies, toothache, yellow fever, inflammation and diabetes. *Irvingia gabonensis* has also been indicated for the treatment of dysentery in this country [10]. In Laos, the bark or wood is grilled on fire, boiled in salty water and drunk to obtain relief from various diseases (Table 1) [9, 25].

Table 1. Traditional uses of *Irvingia* spp.

Country of use	Plant organs used / Route of administration	Traditional uses	Species	Common names	References
Benin	Leaves	Used to treat icterus	*Irvingia gabonensis* (Aubry-Lecomte ex O'Rorke) Baill	Aslotin	[24]
Cameroon	Seed/oral administration	The seeds are used as condiments and the decoction is administered (a bowlful 2 times a day until recovery) to reduce the body weight	-*Irvingia gabonensis* (Aubry-Lecomte ex O'Rorke) Baill -*Irvingia wombolu* Vermoesen (Syn: *Irvingia tenuinucleata* Tiegh.)	bojep	[8, 22]
Gabon	Bark / leaves	The bark decoction is used in a bath to treat asthenia. For children the leaves are pounded and mixed with food.	*Irvingia grandtfolia* (Engl.) Engl	Mulenda	[23]
Laos	Bark / Wood	The bark or wood is grilled on fire and boiled with salt in water and administered orally to overcome tuberculosis related symptoms.	*Irvingia malayana* Oliver ex Bennett	Bohk; Yarr/ Niharr	[9, 25]
Nigeria	-Fruit, bark, seeds and roots -Fruit and bark	-These organs are used as food and to get relief from dysentery, diarrhea toothache and diabetes; -These organs are used to relieve dysentery, diarrhea toothache and diabetes.	-*Irvingia gabonensis* (Aubry-Lecomte ex O'Rorke) Baill. -*Irvingia tenuinucleata* Tiegh. *Irvingiaceae*	-Bush mango, Oro, dika nut tree, Ugiri, Goron, Biri and Apon -Bush mango, Oro	[10]

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4. Phytochemistry of *Irvingia* spp.

Previous phytochemical screening of *Irvingia gabonensis* and *Irvingia wombolu* peels, seed coats, leaves and seeds revealed the presence of alkaloids, flavonoids, tannins, steroids and saponins [26]. Other studies [13] also confirm the presence of saponins, tannins, alkaloids and phenolic compounds in *Irvingia gabonensis.* In a study published by Kuete et al. [27], a number of antimicrobial compounds, including 3-friedelanone (**1**), betulinic acid (**2**), oleanolic acid (**3**), 3,3′,4′-tri-O-methylellagic acid (**4**), 3,4-di-O-methylellagic acid (**5**) and hardwickiic acid (**6**) were isolated and characterized from the stem bark of *Irvingia gabonensis* (Figure 1, Table 2).

In addition, 3-friedelanone (**1**), betulinic acid (**2**), oleanolic acid (**3**), 3,3′,4′-tri-O-trimethylellagic acid (**4**), hardwickiic acid (**6**), methyl gallate (**7**) and 3-β-acetoxyursolic acid (**8**) were isolated and characterized from the methanol extract of *Irvingia gabonensis* [28]. From *Irvingia malayana*, Papers [29] isolated and characterized betulinic acid (**2**), a compound that was already identified in *Irvingia gabonensis* by Kuete et al. [27] and Donfack et al. [28]. Atawodi [30] reported the presence of the phenolic compounds ellagic acid (**9**), methyl gallate (**7**), and dimethoxyellagic acid (**10**) in *Irvingia gabonensis* seeds [30].

In 2012, Sun and Chen [31] used UHPLC/HRMS analysis to identify the chemical constituents of *Irvingia gabonensis* seeds. Ellagic acid (**9**), mono, di, tri-O-methyl-ellagic acid (**4**) and their glycosides were found to be major components of African mango seeds. In brief, the following compounds were identified: citric acid (1R, 2S) (**10**); citric acid (1R, 2R) (**11**); citric acid (1S, 2S) (**12**); citric acid (1S, 2R) (**13**); hexahydroxydiphenoyl(HHDP)-hexose (**14**); di- hexahydroxydiphenoyl-hexose (**15**); di-O-methyl-ellagic acid hexoside (16); methyl-ellagic acid (**17**); galloyl-HHDP-ellagic acid (18); di-O-methyl-ellagic acid deoxyhexide (**19**); kaemferol 3-O-glucoside (**20**); quercetin 3-O-rhamnoside (**21**); mono-O-methyl ellagic acid deoxyhexoside (**22**); di-O-methyl ellagic acid (**23**); di-O-methyl ellagic acid-O-pentoside (**24**); rhamnetin (**25**); di- hexahydroxydiphenoyl -ellagic acid (**26**); di-O-methyl-ellagic acid deoxyhexoside (**27**); galloyl-hexahydroxydiphenoyl-methyl-ellagic acid (**28**); tri-O-methyl-ellagic acid (**29**); mono-O-methyl-ellagic acid rhamnoside (**30**); mono-O-methyl-ellagic acid rhamnosyl-rhamnoside (**31**); galloyl-tri-O-methyl-ellagic acid hexoside (**32**); and diosmetin (**33**) [31]. From powdered seeds of African mango (*I. gabonensis*), methyl 2-[2-formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]-propanoate (**34**), 4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]butanoic acid (**35**), 5-(methoxymethyl)-1H-pyrrole-2-carbaldehyde (**36**), 5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde (**37**), methyl-5-hydroxy-2-pyridinecarboxylate (**38**), 5-hydroxy-2-pyridyl methyl ketone (**39**), 5-hydroxymethyl-2-furancarbaldehyde (**40**) and 4-hydroxybenzoic acid (**41**) were isolated and characterized. Among these, three compounds showed hydroxyl radical scavenging activity (compounds **34**, **35** and **39**; ED_{50} values: 16.7, 11.9 and >20 μM, respectively, vs quercetin; 1.3 μM) [32]. More recently, one phenolic compound (ellagic acid) (**9**) and three flavonoids [(quercetrin (**42**), kaempferol (**43**) and apigenin (**44**)] were identified in *Irvingia gabonensis* stem bark by Ojo et al. [33].

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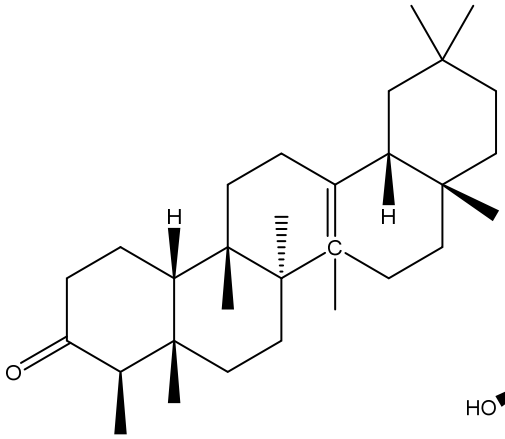
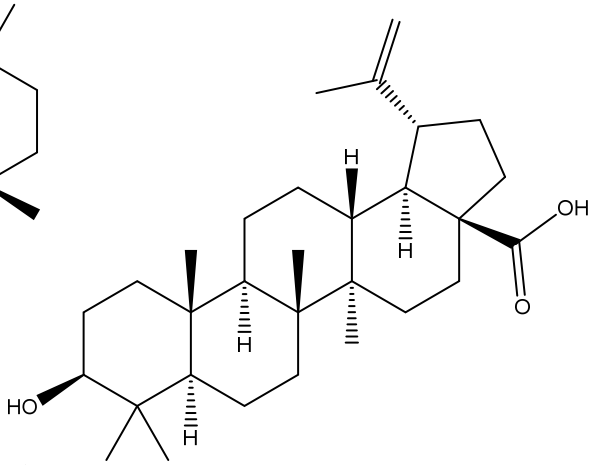
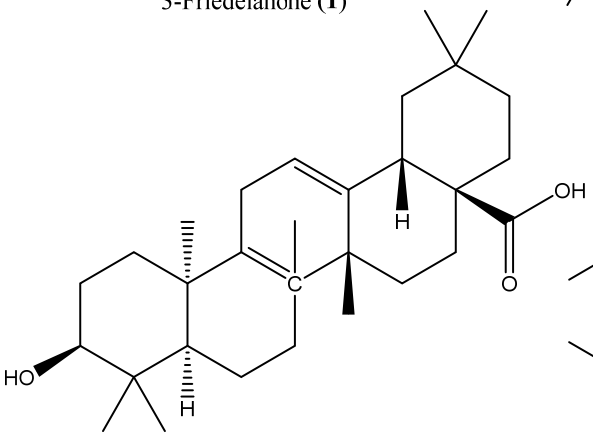


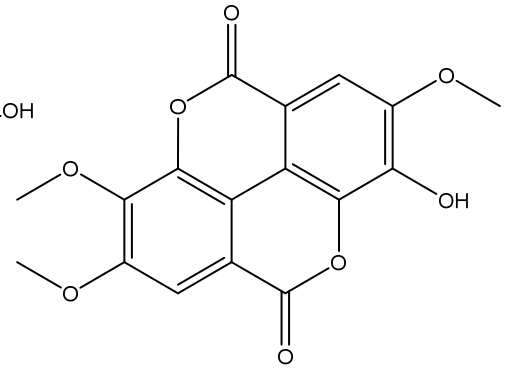
3-Friedelanone (**1**)



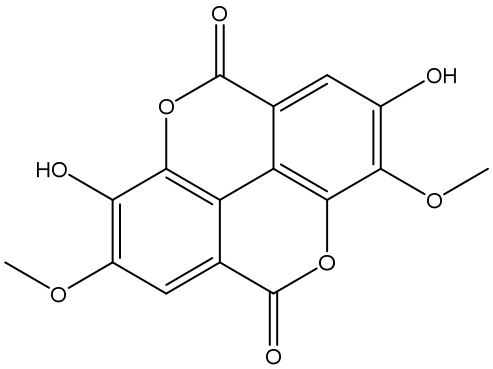
Betulinic acid (**2**)



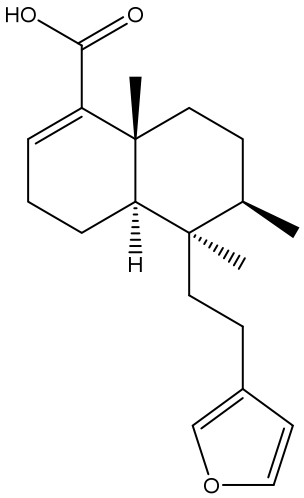
Oleanolic acid (**3**)



3,3',4'- tri-O-methylellagic acid (**4**)



3,4'-di-O-methylellagic acid (**5**)



Hardwickiic acid (**6**)

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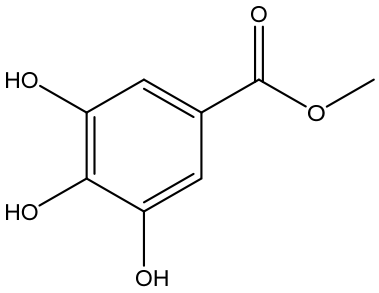
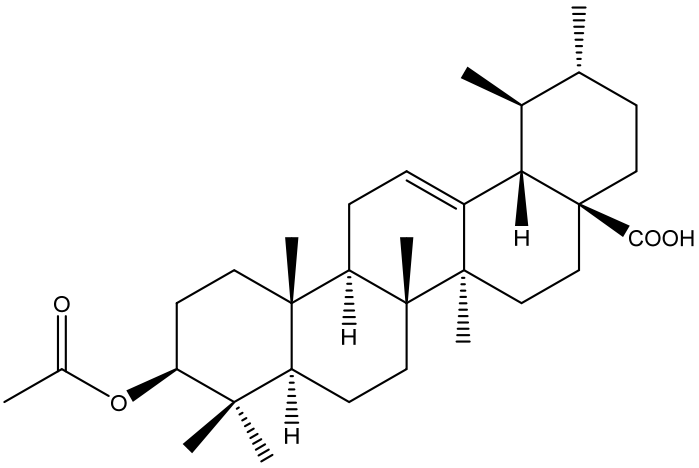
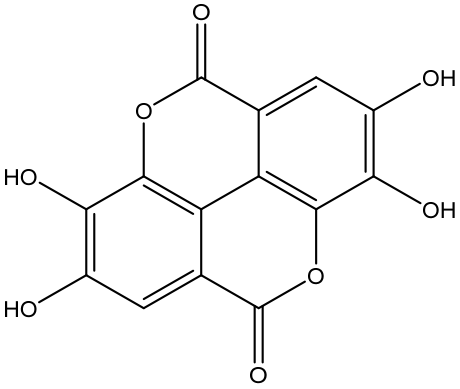


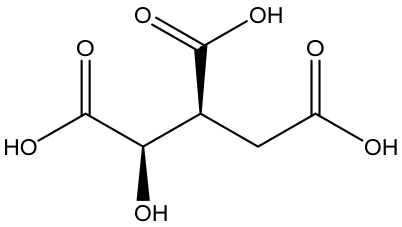
Methyl gallate (**7**)



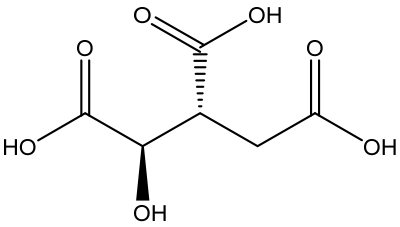
3-beta-Acetoxyursolic acid (**8**)



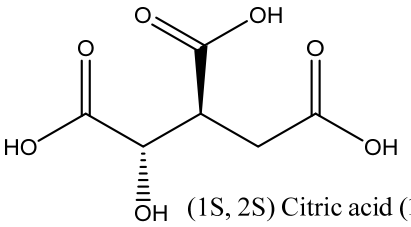
Ellagic acid (**9**)



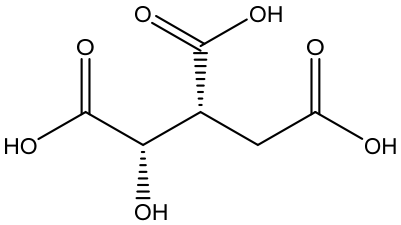
(1R, 2S) Citric acid (**10**)



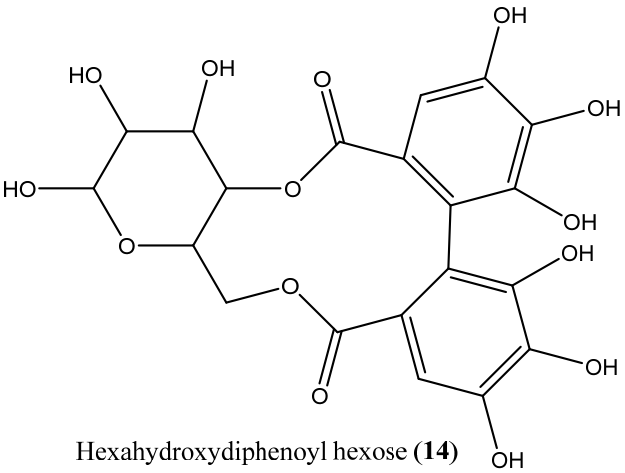
(1R, 2R) Citric acid (**11**)



(1S, 2S) Citric acid (**12**)



(1S, 2R) Citric acid (**13**)



Hexahydroxydiphenoyl hexose (**14**)

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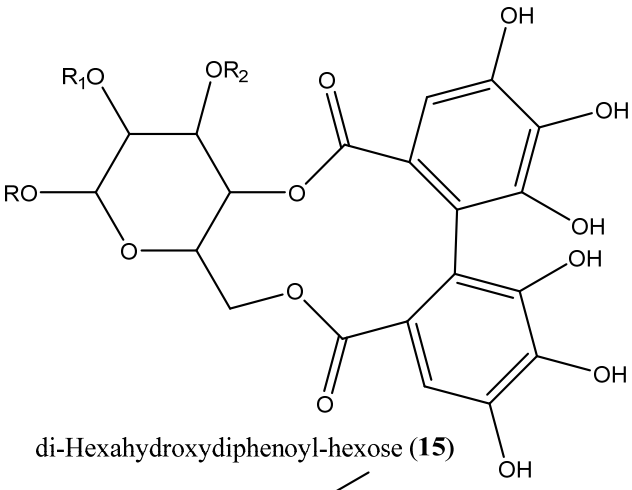
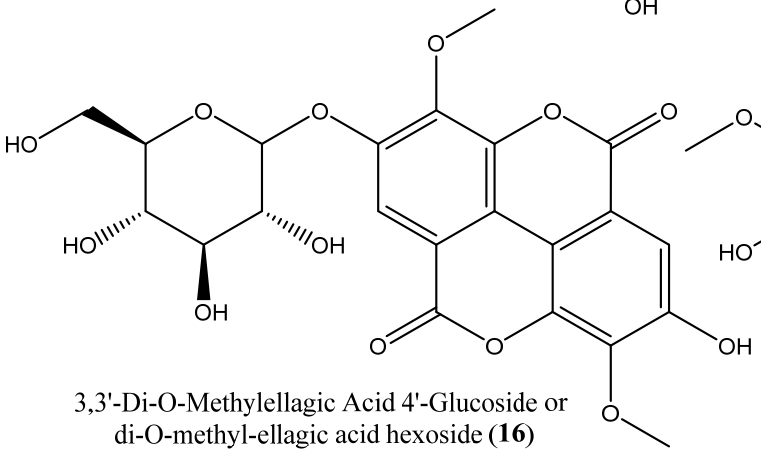
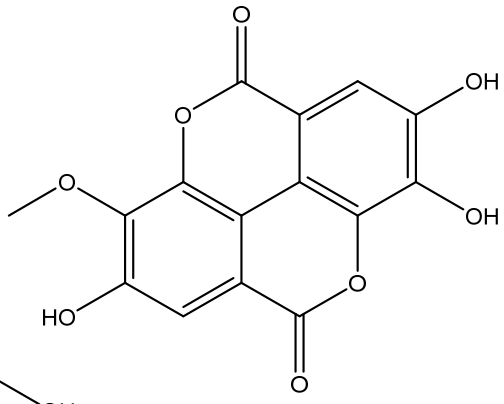


R	R_1	R_2
Hexose	H	H

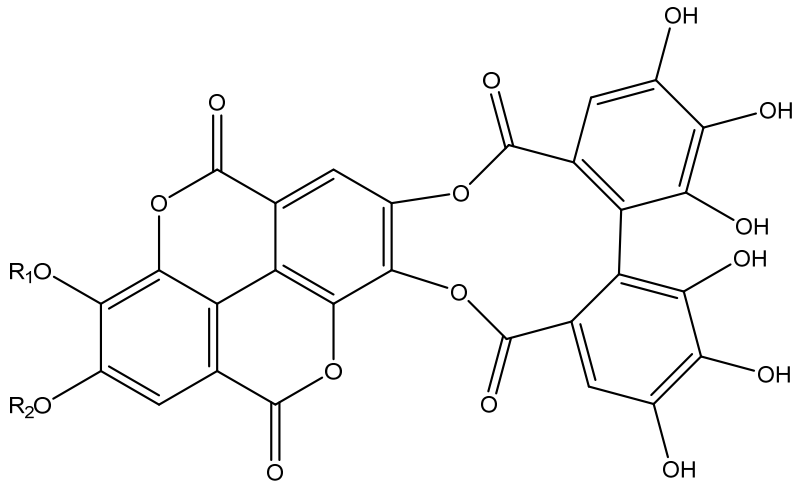
di-Hexahydroxydiphenoyl-hexose (**15**)



3,3'-Di-O-Methylellagic Acid 4'-Glucoside or
di-O-methyl-ellagic acid hexoside (**16**)



Methyl-ellagic acid or
3-O-methylellagic acid (**17**)



R_1	R_2
Galloyl	H

Galloyl-HHDP-ellagic acid (**18**)

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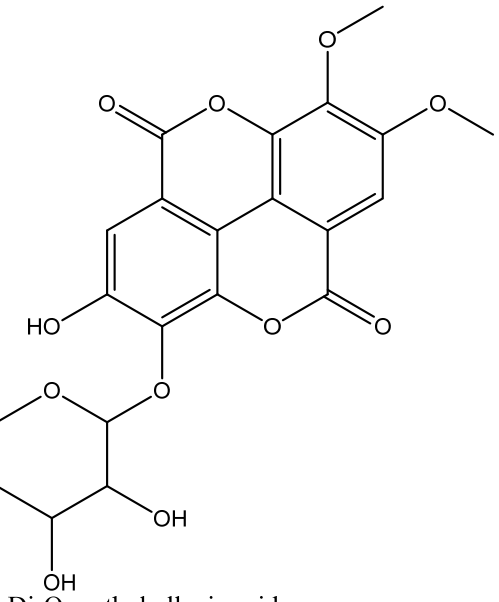
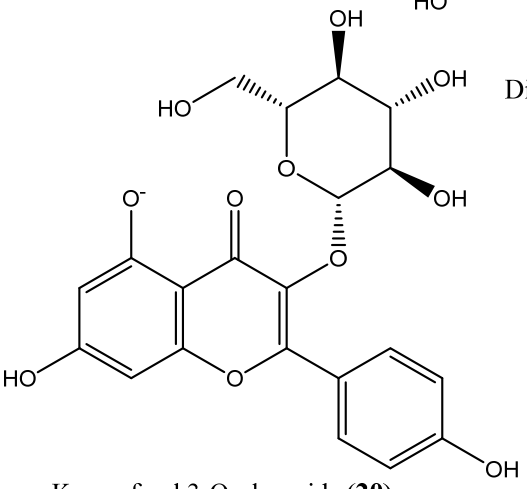
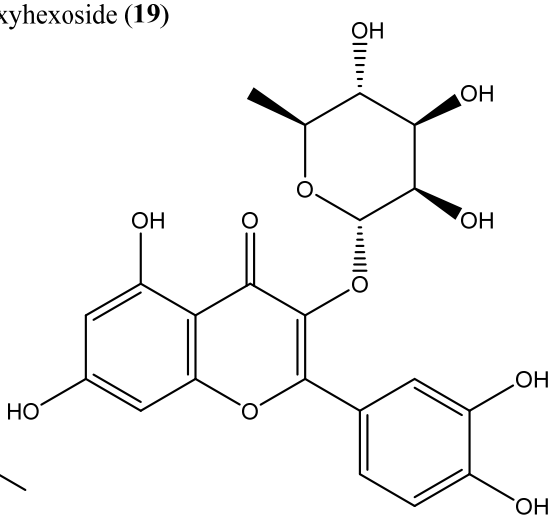


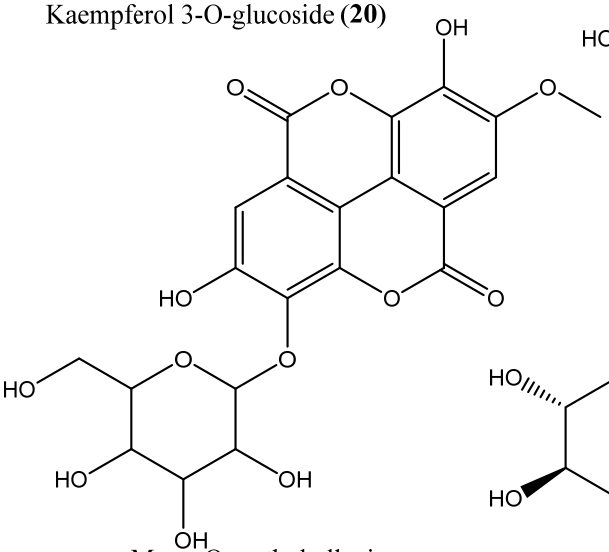
Di-O-methyl-ellagic acid deoxyhexoside (**19**)



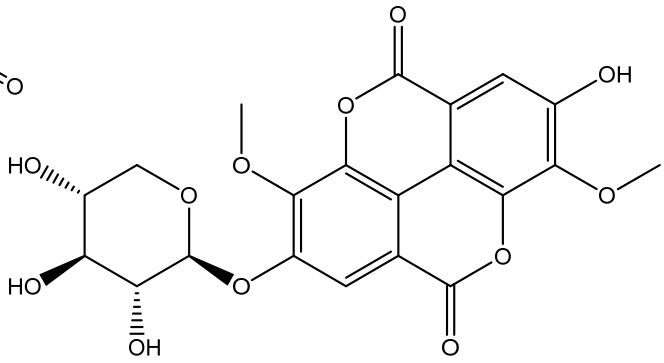
Kaempferol 3-O-glucoside (**20**)



Quercetin 3-O-rhamnoside (**21**)



Mono-O-methyl-ellagic acid deoxyhexoside (**22**)



di-O-Methyl ellagic acid (**23**)

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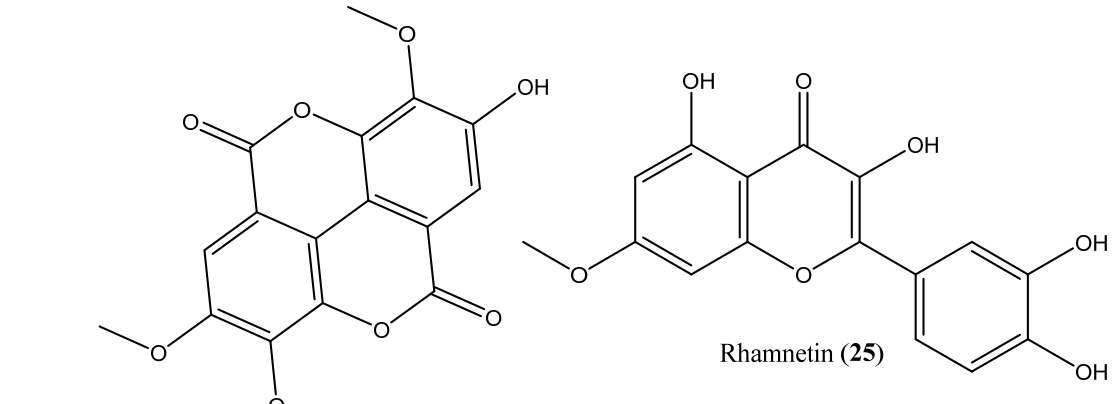
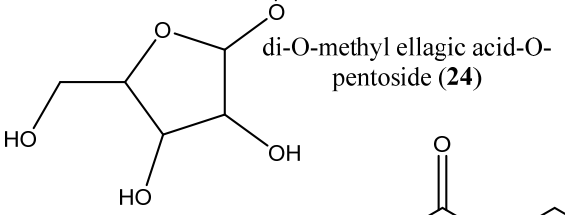
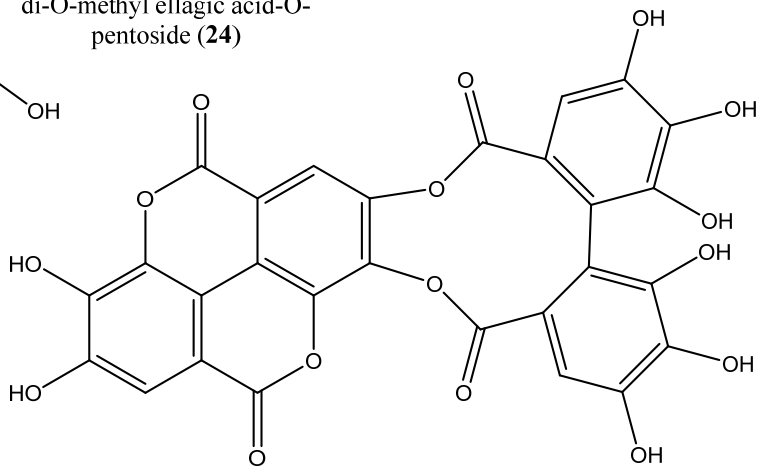


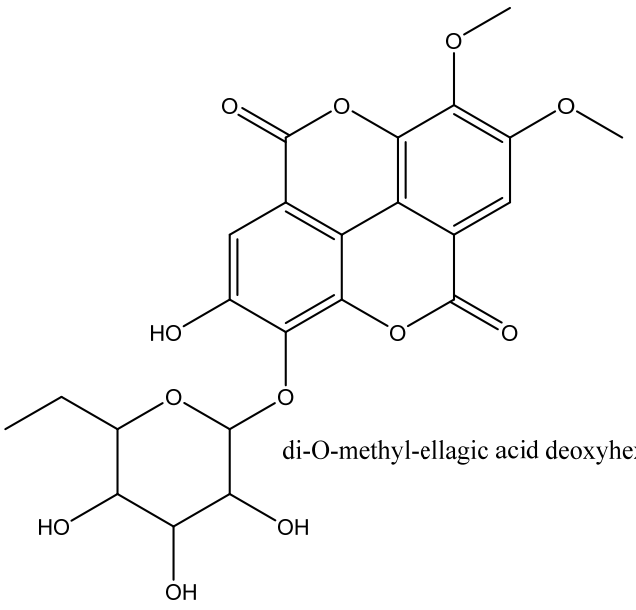
Rhamnetin (**25**)



di-O-methyl ellagic acid-O-pentoside (**24**)



di-Hexahydroxydiphenoyl-ellagic acid (**26**)



di-O-methyl-ellagic acid deoxyhexoside (**27**)

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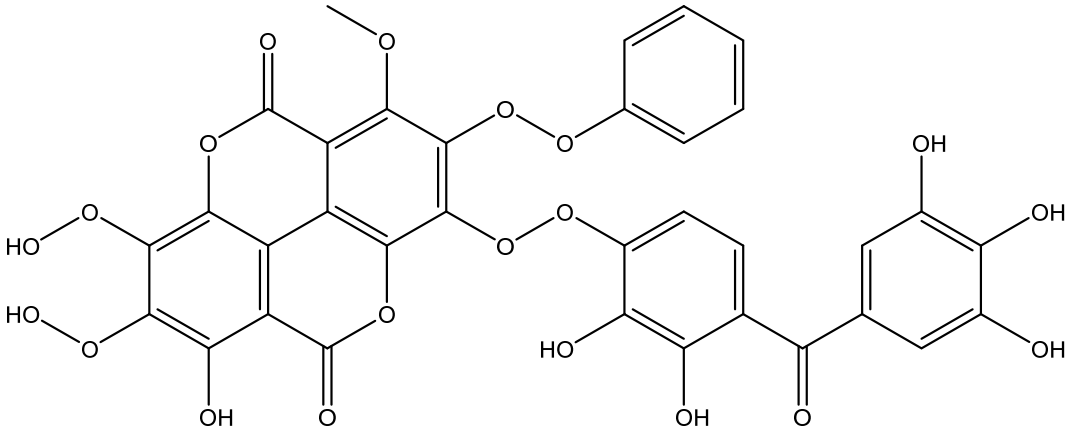
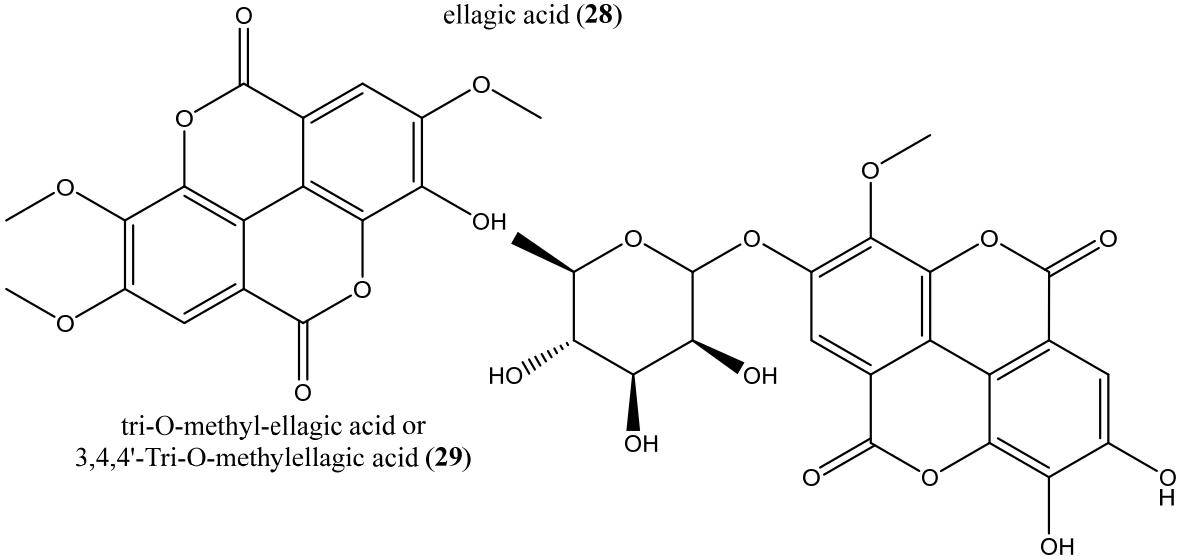
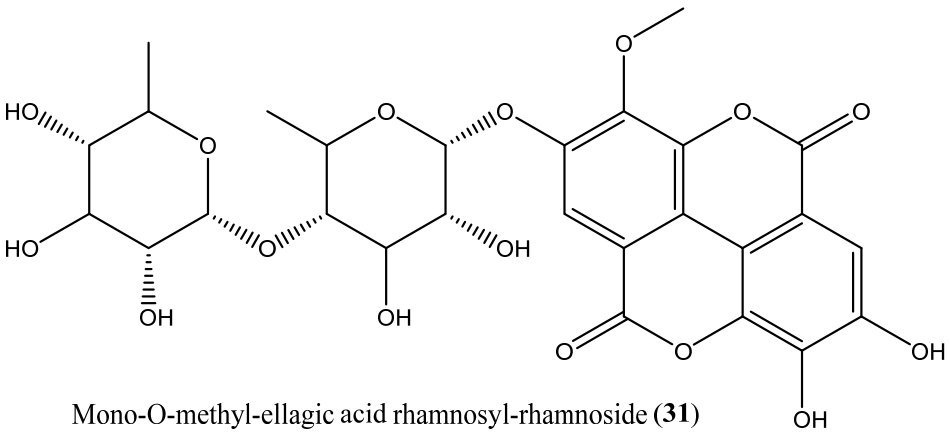


Galloyl-hexahydroxydiphenoxyl-methyl-ellagic acid (**28**)



tri-O-methyl-ellagic acid or 3,4,4'-Tri-O-methylellagic acid (**29**)

Mono-O-methyl-ellagic acid rhamnoside (**30**)



Mono-O-methyl-ellagic acid rhamnosyl-rhamnoside (**31**)

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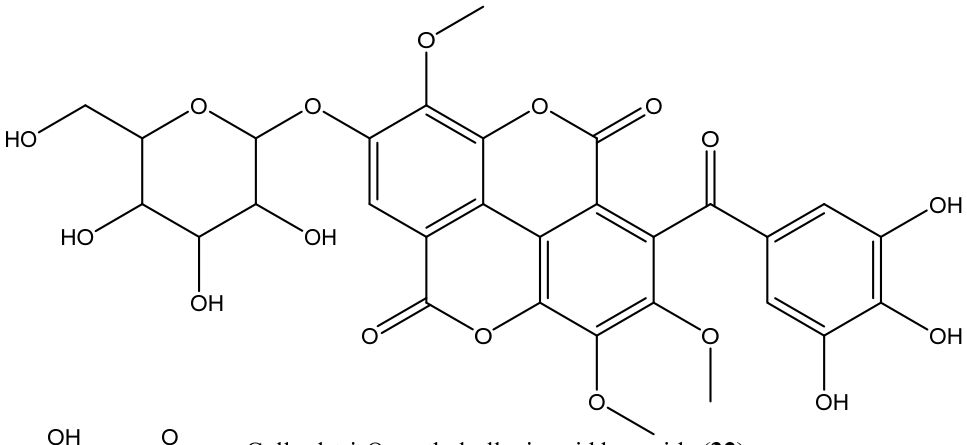
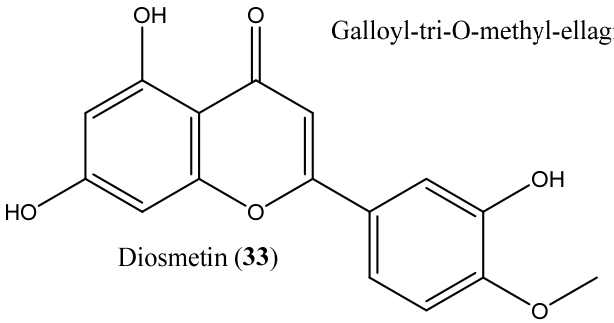
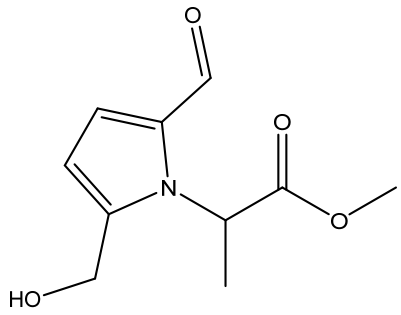


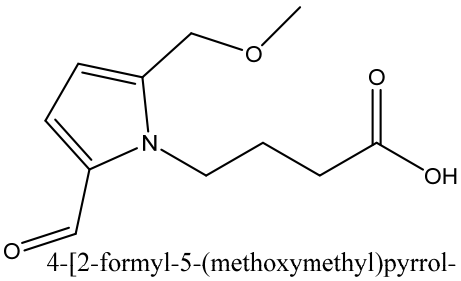
Galloyl-tri-O-methyl-ellagic acid hexoside (**32**)



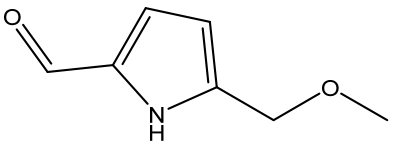
Diosmetin (**33**)



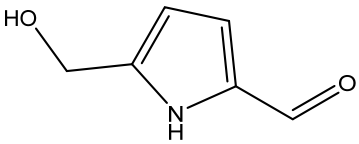
methyl 2-[2-formyl-5- (hydroxymethyl)-1H-pyrrol-1-yl]propanoate (**34**)



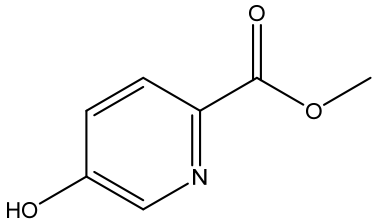
4-[2-formyl-5-(methoxymethyl)pyrrol-1-yl]butanoic acid (**35**)



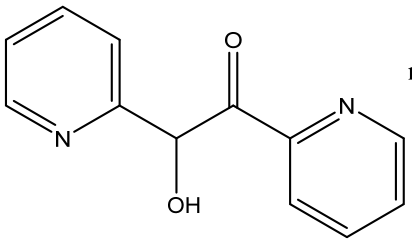
5-(methoxymethyl)-1H-pyrrole-2-carbaldehyde (**36**)



5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde (**37**)



methyl 5-hydroxypyridine-2-carboxylate (**38**)



Hydroxy-2-pyridylmethyl 2-pyridyl ketone (**39**)

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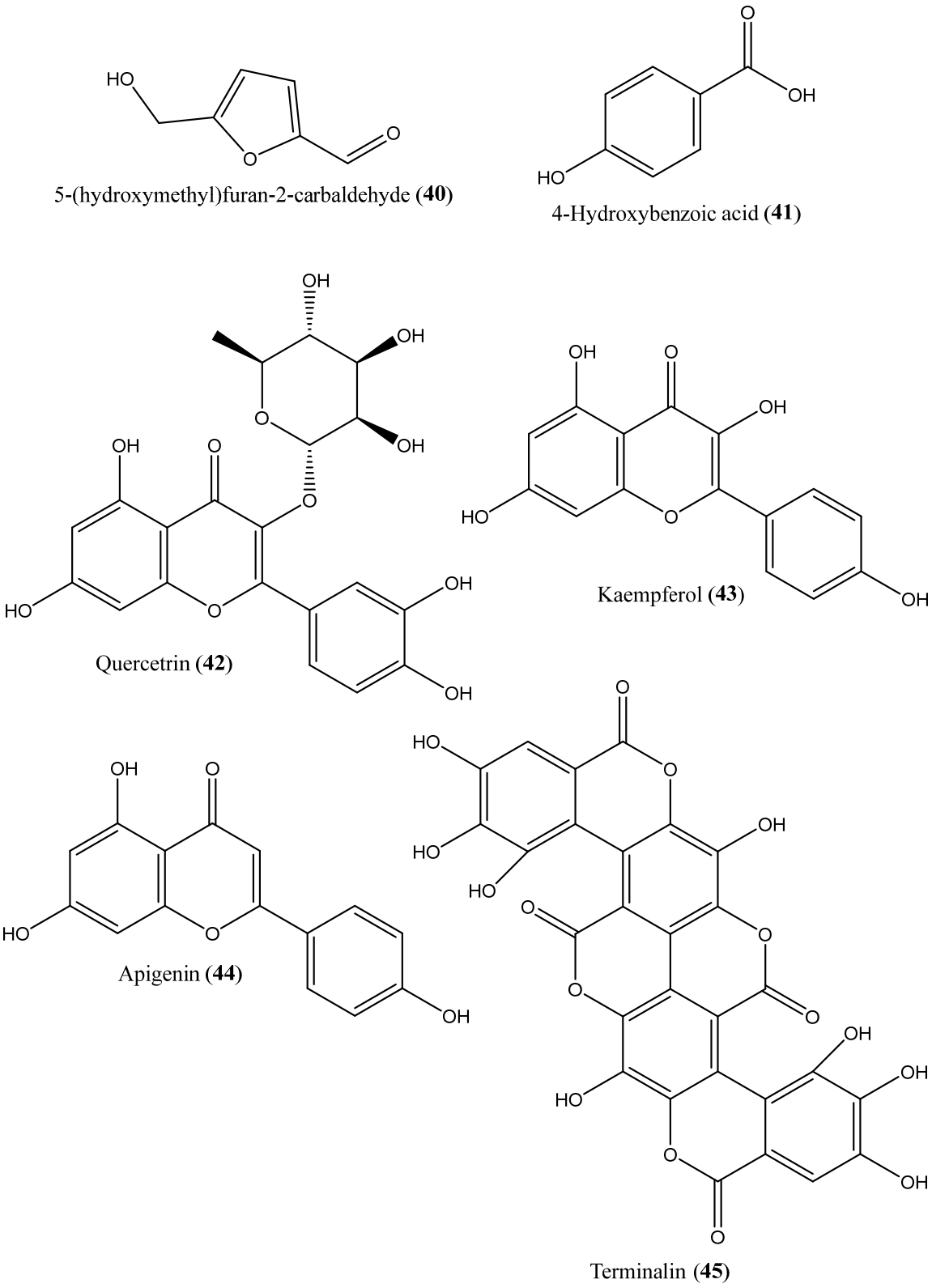

Figure 1. Chemical structures of compounds isolated thus far from *Irvingia* spp.

Table 2. Chemical compounds isolated thus far from *Irvingia* spp.

Serial number	Phytochemical classification	Compound name	Plant species	Plant organs	Reference
1	Triterpenoid	3-Friedelanone (**1**)	*Irvingia gabonensis*	Stem bark	[27, 28]
2	Triterpenoid	Betulinic acid (**2**)	*Irvingia gabonensis*; *Irvingia malayana*	Stem bark	[27, 28, 29]
3	Triterpenoid	Oleanolic acid (**3**)	*Irvingia gabonensis*	Stem bark	[27, 28]
4	Phenolic	3,3′,4′-tri-O-methylellagic acid (**4**)	*Irvingia gabonensis*	Stem bark, seeds,	[27, 28, 31]
5	Phenolic	3,4-di-O-methylellagic acid (**5**)	*Irvingia gabonensis*	Stem bark	[27, 28]
6	Diterpenoid	Hardwickiic acid (**6**)	*Irvingia gabonensis*	Stem bark	[27, 28]
7	Phenolic acid	Methyl gallate (**7**)	*Irvingia gabonensis*	Seeds,	[28, 30]
8	Pentacyclic triterpenoid	3-β-Acetoxyursolic acid (**8**)	*Irvingia gabonensis*		[28]
9	Phenolic compound	Ellagic acid (**9**)	*Irvingia gabonensis*	Seeds, stem bark	[31, 33]
10	Organic acid	Citric acid (1R, 2S) (**10**)	*Irvingia gabonensis*	Seeds	[31]
11	Organic acid	Citric acid (1R, 2R) (**11**)	*Irvingia gabonensis*	Seeds	[31]
12	Organic acid	Citric acid (1S, 2S) (**12**)	*Irvingia gabonensis*	Seeds	[31]
13	Organic acid	Citric acid (1S, 2R) (**13**)	*Irvingia gabonensis*	Seeds	[31]
14	Ose	Hexahydroxydiphenoyl(HHDP)-hexose (**14**)	*Irvingia gabonensis*	Seeds	[31]
15	Ose	di-Hexahydroxydiphenoyl-hexose (**15**)	*Irvingia gabonensis*	Seeds	[31]
16	Ellagitannin	di-O-Methyl-ellagic acid hexoside (**16**)	*Irvingia gabonensis*	Seeds	[31]
17	Phenolic	Methyl-ellagic acid **(17)**	*Irvingia gabonensis*	Seeds	[31]
18	Ellagitannin	Galloyl-HHDP-ellagic acid (**18**)	*Irvingia gabonensis*	Seeds	[31]
19	Ellagitannin	Di-O-methyl-ellagic acid deoxyhexoside (**19**)	*Irvingia gabonensis*	Seeds	[31]
20	Flavonoid	Kaempferol 3-O-glucoside (**20**)	*Irvingia gabonensis*	Seeds	[31]
21	Flavonoid	Quercetin 3-O-rhamnoside (**21**)	*Irvingia gabonensis*	Seeds	[31]
22	Phenolic	Mono-O-methyl ellagic acid deoxyhexoside (**22**)	*Irvingia gabonensis*	Seeds	[31]
23	Phenolic	Di-O-methyl ellagic acid (**23**)	*Irvingia gabonensis*	Seeds	[31]
24	Phenolic	Di-O-methyl ellagic acid-O-pentoside (**24**)	*Irvingia gabonensis*	Seeds	[31]
25	Flavonoid	Rhamnetin (**25**)	*Irvingia gabonensis*	Seeds	[31]
26	Phenolic	Di-hexahydroxydiphenoyl-ellagic acid (**26**)	*Irvingia gabonensis*	Seeds	[31]
27	Phenolic	di-O-Methyl-ellagic acid deoxyhexoside (**27**)	*Irvingia gabonensis*	Seeds	[31]
28	Phenolic	Galloyl-hexahydroxydiphenoyl-methyl-ellagic acid (**28**)	*Irvingia gabonensis*	Seeds	[31]
29	Phenolic	tri-O-Methyl-ellagic acid (**29**)	*Irvingia gabonensis*	Seeds	[31]

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Serial number	Phytochemical classification	Compound name	Plant species	Plant organs	Reference
30	Phenolic	Mono-O-methyl-ellagic acid rhamnoside (**30**)	*Irvingia gabonensis*	Seeds	[31]
31	Phenolic	Mono-O-methyl-ellagic acid rhamnosyl-rhamnoside (**31**)	*Irvingia gabonensis*	Seeds	[31]
32	Phenolic	Galloyl-tri-O-methyl-ellagic acid hexoside (**32**)	*Irvingia gabonensis*	Seeds	[31]
33	Flavonoid	Diosmetin (**33**)	*Irvingia gabonensis*	Seeds	[31]
34	Carboxylate	Methyl 2-[2-formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]-propanoate (**34**)	*Irvingia gabonensis*	Seeds	[32]
35	Carboxylic acid	4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]butanoic acid (**35**)	*Irvingia gabonensis*	Seeds	[32]
36	Carbaldehyde	5-(Methoxymethyl)-1H-pyrrole-2-carbaldehyde (**36**)	*Irvingia gabonensis*	Seeds	[32]
37	Carbaldehyde	5-(Hydroxymethyl)-1H-pyrrole-2-carbaldehyde (**37**)	*Irvingia gabonensis*	Seeds	[32]
38	Carbaldehyde	Methyl-5-hydroxy-2-pyridinecarboxylate (**38**)	*Irvingia gabonensis*	Seeds	[32]
39	Ketone	5-Hydroxy-2-pyridyl methyl ketone (**39**)	*Irvingia gabonensis*	Seeds	[32]
40	Furan	5-Hydroxymethyl-2-furancarbaldehyde (**40**)	*Irvingia gabonensis*	Seeds	[32]
41	Phenolic	4-Hydroxybenzoic acid (**41**)	*Irvingia gabonensis*	Seeds	[32]
42	Flavonoid	Quercetrin (**42**)	*Irvingia gabonensis*	Stem bark	[33]
43	Flavonoid	Kaempferol (**43**)	*Irvingia gabonensis*	Stem bark	[33]
44	Flavonoid	Apigenin (**44**)	*Irvingia gabonensis*	Stem bark	[33]
45	Tannin	Terminalin (**45**)	*Irvingia gabonensis*	Seeds	[34]

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5. Pharmacological activity of *Irvingia* plants

5.1. Antiprotozoal activity

As protozoan diseases are a major threat to human health, medicinal plants have long been used to cure such ailments. It has also been reported that such plants possess a number of antiprotozoal hit compounds. Various organs of *Irvingia gobonensis* (antiplasmodial and anti-*Trypanosoma brucei*), *Irvingia malayana* (antiplasmodial) and *Irvingia grandifolia* (antileishmanial) have been reported to exhibit antiprotozoal activity (Table 3). In fact, studies by Atindehou et al. [35] demonstrated the effectiveness of the crude ethanol extract of *Irvingia gabonensis* stem bark against *Plasmodium falciparum* strain K1 (resistant to chloroquine and pyrimethamine) and *Trypanosoma brucei* rhodesiense with IC_{50} values of 8 and >5 μg/ml vs suramin (IC_{50}: 0.010 μg/ml) and chloroquine (IC_{50}: 0.064 μg/ml), respectively [35]. In 2007, Nguyen-Pouplin et al. [36] obtained IC_{50} values of 5.0 μg/ml and 10.5 μg/ml for methanol and ethanol extracts of *Irvingia malayana*, respectively (vs chloroquine; IC_{50}: 0.1 μM), upon testing against the chloroquine-resistant FcB1/Colombia strain of *Plasmodium falciparum*. Regarding cytotoxicity experiments, methanol and ethanol extracts were not cytotoxic toward HeLa cells (IC_{50}: 14.8 and 11.7 μg/ml; SI: 2.9 and 1.1, respectively). Against MRC5 cells, the methanol extract yielded an IC_{50} value of 50.5 μg/ml (SI: 10) (Nguyen-Pouplin et al. [36]).

In an *in vivo* study, Agubata et al. [37] revealed the antiplasmodial activity of *Irvingia gabonensis* fats and homolipid-based artemether microparticles combined with *Irvingia gabonensis* in *Plasmodium berghei*-infected mice. In fact, the oral administration of *Irvingia gabonensis* fat (AD), and microparticle capsules of artemether (4 mg/kg) combined with I. gabonensis lipid matrices (LM) and phospholipon1 90G (P90G) [ADP3 (3:1), ADP4 (4:1) and ADP9 (9:1)] led to a significant inhibition of the parasite (percent inhibition: 83.84, 83.68, 82.63 and 87.37%, respectively) compared to artemether treatment (percent inhibition: 56.32%) [37]. Furthermore, Lamidi et al. [38] demonstrated the *in vitro* antileishmanial activity of methanol, methanol/water (50:50) and dichloromethane extracts from the stem bark and leaves with a common IC_{50} value (100 μg/ml). However, methanol, methanol/waterF (50:50) and dichloromethane extracts from the stem bark (IC_{50} values: 7.7, 8.4, and 8.3 μg/ml, respectively) and leaves (IC_{50} values: >100, 6.2 and 5.4 μg/ml, respectively) of *I. grandifolia* were cytotoxic when tested against Vero cells [38]. Previous studies have demonstrated the presence of steroids, flavonoids, alkaloids, cardiac glycosides, volatile oils, terpenoids, tannins, saponins, etc. in *Irvingia* plants [39].

Secondary metabolites, such as flavonoids, have been proven to inhibit the growth of several protozoan parasites, including *Trypanosoma* spp. and *Leishmania* spp. [40]. In fact, flavonoids are capable of binding to the C-terminal nucleotide-binding domain of the P-glycoprotein-like transporter in *Leishmania* spp. (a transporter involved in parasite multidrug resistance). This class of secondary metabolites works as inhibitors of enzymes, or proteins that are crucial for the survival and virulence of certain Trypanosomatidae. These enzymes include DNA topoisomerases, protein tyrosine kinase and squalene synthase. Flavonoids have been shown to induce apoptosis of host cells, such as epithelial cells [41], or by direct induction of apoptosis of the parasite [42, 43].

Table 3. Antiprotozoal activity of plants from the genus Irvingia.

Irvingia spp.	Extracts/ Compounds	Model of the study	Significant results	Toxicity/ Cytotoxicity	Type of screening	Reference
Irvingia gabonensis	Crude ethanol extract of the stem bark	-*Plasmodium falciparum* strain K1 -*Trypanosoma brucei rhodesiense*	-IC_{50}: >5 µg/ml, vs chloroquine (IC_{50}: 0.064 µg/ml); -IC_{50}: 8 µg/ml, vs suramin (IC_{50}: 0.010 µg/ml).	NS	Alamar Blue assay	[35]
Irvingia malayana Oliv. ex Benn.	Methanol and ethanol (80%) extract from the leaves	-Chloroquine-resistant FcB1/Colombia strain of *Plasmodium falciparum* -Cytotoxicity: The human cervix carcinoma cells (HeLa), and the human diploid embryonic lung cells (MRC5).	IC_{50}: 5.0 and 10.5 µg/ml for methanol and ethanol extracts, respectively vs chloroquine (IC_{50}: 0.1 µM) on	**Cytotoxicity** *Methanol extract -HeLa cells; IC_{50}: 14.8 µg/ml and SI: 2.9; -MRC5 cells: IC_{50}: 50.5 µg/ml and SI: 10.0. *Ethanol extract -HeLa cells; IC_{50}: 11.7 µg/ml and SI: NT; -MRC5 cells: IC_{50}: 1.1 µg/ml and SI: NT.	**Antiplasmodial test:** [3H]Hypoxanthine Uptake Assay; -**Cytotoxicity:** methyl thiazole tetrazolium (MTT) assay	[36]
Irvingia gabonensis var. excelsa (Irvingia wombolu)	Microparticles prepared from fatty acids from the nuts of *Irvingia gabonensis,* extracted using petroleum ether (microparticles composed of artemether (4 mg/kg), lipid matrices (LM) and phospholipon1 90G (P90G) [ADP3 (3:1), ADP4 (4:1) and ADP9 (9:1)])	*Plasmodium berghei*-infected mice	Percentage of inhibition of *Plasmodium berghei*: 83.84, 83.68, 82.63 and 87.37% for ADP3 (3:1), ADP4 (4:1) and ADP9 (9:1), respectively vs artemether treatment alone (percent inhibition: 56.32%) inhibition: 56.32%)	NS	Four day suppressive test	[37]
Irvingia grandifolia	Methanol, methanol/water (50:50), and dichloromethane extracts prepared from stem barks and leaves	Promastigote form of *Leishmania Infantum*; Cytotoxicity on Human cell line (Vero cells)	IC_{50}: >100 µg/ml for the extracts assayed.	**Cytotoxicity** *Stem bark: IC_{50} :7.7, 8.4 and 8.3 µg/ml respectively for the extracts, respectively; *Leaves: IC_{50}: >100, 6.2, and 5.4 µg/ml for the extracts, respectively.	Cell viability test	[38]

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5.2. Antimicrobial activity

According to the literature, numerous studies have demonstrated the antimicrobial activity of plants from the genus *Irvingia* (Table 3). One such study is that of Osadebe and Ukwueze [44], who reported the antibacterial activity (MIC values: 4.31, 3.53, 5.53 and 5.55 µg/ml, respectively) of petroleum ether extract from *Irvingia gabonensis* leaves against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Salmonella typhi*. Moreover, Kuete et al. [27]evaluated the *in vitro* antimicrobial activity of methanol extract, fractions (A, B and C), and compounds [3-friedelanone (**1**), betulinic acid (**2**), oleanolic acid (**3**), 3,3′,4′-tri-O-methylellagic acid (**4**), 3,4-di-O-methylellagic acid (**5**) and hardwickiic acid (**6**)] from the stem bark of *Irvingia gabonensis* on 22 species of microorganisms, including bacteria [*Citrobacter freundii* (MICs: 78.12, > 312.50,19.53, 39.06, > 312.50, > 312.50, > 312.50, 78.12, 39.06, and 19.53 µg/ml); *Enterobacter aerogens* (MICs: 78.12, 156.25, 78.12, 156.25, 312.50, 312.50, 312.50, 78.12, 19.53, and 78.12 µg/ml); *Enterobacter cloacae* (MICs: 78.12, 156.25, 19.53, 9.76, 312.50, 312.50, 312.50, 19.53, 9.76, and 4.88 µg/ml); *Escherichia coli* (MIC values: 156.25, 78.12, 4.88, 19.53, 156.25, 78.12, 78.12, 9.76, 9.76, and 19.53 µg/ml); *Klebsiella pnemoniae* (MICs: 156.25, 78.12, 9.76, 19.53, 78.12, 78.12, 39.06, 39.06, 19.53 and 39.06 µg/ml); *Morganella morganii* (MICs: 78.12, 312.50, 39.06, 9.76, 312.50, 312.50, 312.50, 39.06, 19.53, and 4.88 µg/ml); *Neisseria gonorrhea* (MICs: 39.06, 9.76, 4.88, NT, > 312.50, > 312.50, 19.53, 9.76, 1.22 µg/ml); Pr*oteus mirabilis* (MICs: 78.12, NT, 19.53, 39.06, > 312.50, > 312.50, > 312.50, 39.06, 19.53, and 39.06 µg/ml); *Proteus vulgaris* (MICs: 78.12, > 312.50, 4.88, 9.76, > 312.50, > 312.50, > 312.50, 9.76, 9.76 and 19.53 µg/ml) ; *Proteus aeruginosa* (MICs: 78.12, > 312.50, 9.76, 9.76, > 312.50, > 312.50, > 312.50, 19.53, 4.88, 19.53 µg/ml); *Shigella dysenteriae* (MICs: 78.12, 156.25, 39.06, 19.53, 312.50, 312.50, 156.25, 78.12, 9.76 and 78.12 µg/ml); *Shigella flexneri* (MICs: 312.50, 312.50, 9.76, 9.76, 312.50, > 312.50, 312.50, 4.88, 4.88 and 4.88 µg/ml) *Salmonella typhi* (MICs: 312.50, > 312.50, 39.06, 9.76, > 312.50, > 312.50, > 312.50, 78.12, 9.76, and 4.88 µg/ml) *Streptococcus faecalis* (MIC values: 156.25, 312.50, 39.06, 78.12, > 312.50, > 312.50, > 312.50, 78.12, 78.12, and 39.06 µg/ml); *Staphylococcus aureus* (MICs: 78.12, 312.50, 78.12, 19.53, 312.50, > 312.50, 312.50, 78.12, 19.53, and 19.53 µg/ml); *Bacillus cereus* (MICs: 156.25, > 312.50, 19.53, 9.76, > 312.50, > 312.50, > 312.50, 39.06, 19.53, and 4.88 µg/ml); *Bacillus megaterium* (MICs: 156.25, > 312.50, 19.53, 9.76, > 312.50, > 312.50, > 312.50, 156.25, 39.06, and 4.88 µg/ml); *Bacillus stearotherm* (MICs: 78.12, > 312.50, 19.53, 4.88, > 312.50, > 312.50, > 312.50, 78.12, 9.76, and 4.88 µg/ml); *Bacillus subtilis* (MICs: 156.25, NT, 39.06, 9.76, > 312.50, > 312.50, > 312.50, 156.25, 9.76 and 4.88 µg/ml), respectively vs gentamicin (MIC range: 0.61 µg/ml-9.76 µg/ml)] and fungi [*Candida albicans* (MICs: 78.12, > 312.50, 19.53, 78.12, > 312.50, > 312.50, > 312.50, 9.76, 78.12, and 39.06 µg/ml); *Candida gabrata* (MICs: 78.12, > 312.50, 39.06, 78.12, > 312.50, > 312.50, > 312.50, 19.53, 39.06, and 39.06 µg/ml); *Candida krusei* (MICs: 156.25, > 312.50, 19.53, 156.25, > 312.50, > 312.50, > 312.50, 9.76, 78.12, and 39.06 µg/ml), respectively vs nystatin (MIC range: 2.44-9.76 µg/ml)] [27]. Furthermore, *Candida albicans* was also inhibited (MIC value: 11.4 µg/ml) by the ethanol extract of *Irvingia malayana*. Interestingly, this extract showed MIC value greater than 100 µg/ml when tested against Vero cells, attesting to its high selectivity (SI: > 8.77) [25]. Two years later, Nworie et al. [45] evaluated the *in vitro* antibacterial activity of hot water, cold water and ethanol extract of *Irvingia gabonensis* leaves and stem bark on *Staphylococcus aureus* and *Escherichia coli* using agar-well diffusion and agar dilution methods. As a result, the diameter of inhibition ranged between 8-23 mm for the ethanol extract, 8-14 mm for the hot water extract and 8-20 mm for the cold water extract. Moreover, the MIC values ranged between 6.25-50 mg/ml [45]. Aqueous, methanol and hexane extracts extracted from *Irvingia gabonensis* leaves were administered to Escher*ichia coli*-induced diarrheal mice at 100 and 200 mg/kg. As a result, the treatment significantly reduced the mouse pathogenic conditions by 80 and 60%, 80 and 80%, and 60 and 40% for aqueous, methanol, and hexane extracts, respectively [46] (Table 4). Wamba et al. [47] demonstrated the anti-staphylococcal activity of the methanol extract of *Irvingia gabonensis* leaves against seven (7) clinical isolates namely SA18, SA23, SA56, SA116, MRSA3, MRSA9 and MRSA11, with an MIC value of 1024 µg/ml [47]. In addition, Olanrewaju et al. [13] assessed the antibacterial activity of the chloroform extract of *I. gabonensis* leaves against a series of bacteria (*Salmonella typhi*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*) and fungi (*Trichophyton rubrum* and *Candida albicans*). Interestingly, the chloroform extract inhibited the

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growth of *S. aureus* and *S. typhi* (MIC: 0.625 mg/mL), *K. pneumonia* and *E. coli* (MIC: 5 mg/mL), *P. aeruginosa* and *S. paratyphi* (MIC: 10 mg/mL), *T. rubrum* (MIC: 10 mg/mL) and *C. albicans* (MIC: 2.5 mg/mL) [13].

More recently, Wandji et al. [48] reported the inhibitory effect of the methanol extract of *I. gabonensis* seeds against *Staphylococcus aureus* and *Fusarium oxysporum* with MIC values of 2 and 6.5 mg/ml, respectively [48].

As reported by Kuete et al. [27], *Irvingia* spp. possess a variety of antimicrobial compounds, such as the triterpenoid 3-friedelanone (**1**) and the phenolic acids betulinic acid (**2**), oleanolic acid (**3**), 3,3′,4′-tri-O-methylellagic acid (4), 3,4-di-O-methylellagic acid (**5**) and hardwickiic acid (**6**) (Table 4). Generally, triterpenoids are reported to exhibit a number of biological activities, such as antibacterial and antifungal activities. In fact, this class of secondary metabolites affects the expression of bacterial genes involved in biofilm formation, peptidoglycan turnover and cell autolysis [49]. Other mechanisms of action of this class of compounds include DNA fragmentation, cell cycle arrest [50] and apoptosis [51]. In addition, the antimicrobial mechanisms of action of phenolic compounds on bacterial cells have been partially attributed to cell membrane damage, inhibition of virulence factors, such as enzymes and toxins, and suppression of bacterial biofilm formation [52].

Table 4. Antimicrobial activity of extracts and compounds from plants of the genus *Irvingia*.

Irvingia spp.	Extracts/ Compounds	Model of the study	Significant results	Toxicity/ Cytotoxicity	Type of screening	Reference
Irvingia gabonensis	Methanol extract, fractions (A, B and C), and compounds [3-friedelanone (**1**), betulinic acid (**2**), oleanolic acid (**3**), 3,3′,4′-tri-O-methylellagic acid (**4**), 3,4-di-O-methylellagic acid (**5**) and hardwickiic acid (**6**)] from the stem bark.	22 species of microorganisms	MIC values: *Fungi: *Candida albicans* (MIC values: 39.06-> 312.50 µg/ml); *Candida gabrata* (MIC values: 19.53-> 312.50 µg/ml); *Candida krusei* (MIC values: 9.76-> 312.50 µg/ml), vs nystatin (2.44-9.76 µg/ml); *Bacteria: *Citrobacter freundii* (MIC range: 19.53-> 312.50 µg/ml); *Enterobacter aerogens* (MICs: 19.53-312.50 µg/ml); *Enterobacter cloacae* (MICs: 9.76-312.50 µg/ml); *Escherichia coli* (MIC range: 4.88-156.25 µg/ml); *Klebsiella pnemoniae* (MICs: 9.76-156.25 µg/ml); *Morganella morganii* (MICs: 4.88-312.50 µg/ml); *Neisseria gonorrhea* (MICs: 1.22 - > 312.50 µg/ml); *Proteus mirabilis* (MICs: 19.53-> 312.50 µg/ml); *Proteus vulgaris* (MICs: 4.88-> 312.50 µg/ml) ; *Proteus aeruginosa* (MIC values: 4.88-> 312.50 µg/ml); *Shigella dysenteriae* (MIC values: 9.76-312.50 µg/ml); *Shigella flexneri* (MICs: 4.88-312.50 µg/ml) *Salmonella typhi* (MICs: 4.88-> 312.50 µg/ml) *Streptococcus faecalis* (MICs: 39.06-> 312.50 µg/ml); *Staphylococcus aureus* (MICs: 19.53-> 312.50 µg/ml); *Bacillus cereus* (MICs: 4.88-> 312.50 µg/ml); *Bacillus megaterium* (MIC range: 4.88-> 312.50 µg/ml); *Bacillus stearotherm* (MICs: 4.88- > 312.50 µg/ml); *Bacillus subtilis* (MICs: 4.88-> 312.50 µg/ml) vs gentamicin (MIC range: 0.61 µg/ml-9.76 µg/ml).	NS	Minimum Inhibitory Concentration (MIC) assays	[27]
Irvingia gabonensis	Leaves/ Petroleum ether extract	*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Salmonella typhi*.	MIC values: 4.31, 3.53, 5.53 and 5.55 µg/ml, for the strains, respectively	NS	Minimum Inhibitory Concentration (MIC) assays	[44]
Irvingia malayana Oliver ex Bennett	Ethanol extract	-Strains *Mycobacterium tuberculosis* H37Rv, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* -Cytotoxicity: Vero cells	Percentage of inhibition at the concentration of 11.4 µg/ml: 19%, 31%, 38%, and 98% against *Mycobacterium tuberculosis* H37Rv, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, respectively.	Ethanol extract: IC_{50}: 100 µg/ml on Vero cells; SI: > 8.77.	Alamar Blue, assay	[25]
Irvingia gabonensis	Hot water, cold water and ethanol extracts prepared from the leaves and stem bark.	*Staphylococcus aureus* and *Escherichia coli*	-Diameter of inhibition: ranging between 8-23 mm, 8-14 mm, and 8-20 mm for the extract, respectively; -MIC range: 6.25-50 mg/ml.	NS	Agar-well diffusion and agar dilution methods	[45]
I. gabonensis	Methanol extract of the seeds	*Staphylococcus aureus* and *Fusarium oxysporum*	MIC values: 2 and 6.5 mg/ml against the tested strains, respectively	NS	Minimum Inhibitory Concentration (MIC) assays	[48]

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5.3. Antioxidant activity

The majority of diseases are intricately related to redox imbalance and oxidative stress. The inhibition of this phenomenon by plant secondary metabolites has proven efficient in reducing the pathogenesis of several diseases. As reported by many authors, the presence of a variety of compounds, such as flavonoids, phenolic compounds, alkaloids, tannins and saponins, among others, in medicinal plants has contributed to reverting oxidative stress in disease pathogenesis. One such plant includes *Irvingia gabonensis*, which has been reported to exhibit antioxidant activity [5, 15, 21, 30, 32, 33, 53, 54]. In brief, Agbor et al. [53] used Folin-Ciocalteu reagent (Folin) and ferric reducing antioxidant power (FRAP) tests to evaluate the antioxidant activity of methanol extract from *Irvingia gabonensis* seeds [53]. In the FRAP assay, the free and total antioxidant capacities were found to be 283.1 and 431.58 mg/g, respectively. In the Folin test, the free and total antioxidant capacities were found to be 7.26 and 10.74 mg/g, respectively. In another experiment, Arogba and Omede [54] described the antiradical scavenging activity of the methanol extract of *Irvingia gabonensis* seeds with an IC_{50} value of 177.22 µg/ml, compared with the activity of vitamin C (IC_{50}: 300.22 µg/ml) and quercetin (184.71 µg/ml) [54]. Three compounds [methyl 2-[2-formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]-propanoate (**34**), 4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]butanoic acid (**35**), and 5-hydroxy-2-pyridyl methyl ketone (**39**)], isolated from the African mango's (*I. gabonensis*) seeds showed hydroxyl radical scavenging activity with ED_{50} values of 16.7, 11.9 and >20 µM, respectively, vs quercetin (ED_{50} value: 1.3 µM) [32]. Atawodi [30] used hypoxanthine/xanthine oxidase and 2-deoxyguanosine assays as models to assess the antioxidant activity (IC_{50} value: 28 µl) and radical scavenging capacity (IC_{50} value: 281 µl), respectively, of the methanol extract of *Irvingia gabonensis* seeds [30]. Moreover, Ewere et al. [5] described the DPPH scavenging power of the ethanol extract of *Irvingia gabonensis* leaves with inhibition percentages ranging from 40 to 95% at 20 to 100 µg/ml [5]. FRAP, DPPH, ABTS tests and acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory assays were used to assess the antioxidant efficacy of the phenol-rich fraction of *Irvingia gabonensis* stem bark with IC_{50} values of 113.10, 18.98, 18.25, 32.90 and 41.50 µg/ml, respectively [33].

The antioxidant efficacy of the ethanol extract of *Irvingia gabonensis* seeds was also confirmed by Olorundare et al. [15] by using DPPH, FRAP and NO scavenging tests. At 25, 50, 75 and 100 µg/ml, this extract inhibited DPPH radicals by 14.59, 43.53, 67.98, and 75.44%, respectively, vs vitamin C (percent inhibition: 45.06, 56.55, 76.92, and 89.83%, respectively). In FRAP (extract: 0.08, 0.13, 0.28 and 0.48%, vs vitamin C: 0.24, 0.38, 0.48, and 0.63 % at 25, 50, 75 and 100 µg/ml, respectively) and NO (13.55, 39.98, 68.39 and 77.09%, vs vitamin C: 47.89, 63.09 76.07, and 84.91%, respectively) tests, the plant extract also displayed significant antioxidant activity [15].

To confirm the antioxidant capacity of methanol, ethanol and phenol-rich extracts from *Irvingia gabonensis* seeds, Nguyen et al. [55] evaluated ferric ion reducing antioxidant power (FRAP), Trolox equivalent antioxidant capacity (TEAC) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and found that these extracts exhibit significant ferric ion reducing power (FRAP values: 0.18, 0.18, and 0.09 mM Fe2+/g for the extracts, respectively); TEAC (3597.11, 3046.60 and 21.38 mM Trolox/g for the extracts, respectively) and DPPH radical scavenging potential (EC_{50}: 2.81 and 2.81 mg/ml for methanol and ethanol extracts, respectively). More recently, the *in vitro* and *in vivo* antioxidant activity of the ethanol extract of *Irvinga gabonensis* leaves was determined by Ewere et al. [21] (Table 5). In *in vitro* tests, the extract presented IC_{50} values of 258.47 and 640.05 µg/ml for nitric oxide and hydrogen peroxide scavenging activities, respectively, vs, ascorbic acid (IC_{50}: 91.95 and 109.72 µg/ml, respectively). Upon *in vivo* studies, the oral administration of the ethanol extract of *Irvingia gabonensis* leaves to arsenic (dose: 4.1 mg/kg)-induced hepatic oxidative stress rats decreased serum ALT, ALP, CAT, MDA and GGT activities and increased SOD and GPx concentrations, suggesting that this extract possesses antioxidant activity [21]. Furthermore, Atanu et al. [16] confirmed the antioxidant activity of aqueous, ethanol, chloroform and *n*-hexane extracts from *Irvingia gabonensis* leaves through DPPH (IC_{50}: 30.74, 21.42, 36.62 and 31.41 µg/ml, respectively), FRAP (23.91, 22.25, 22.43 and 11.57 mM Fe2+ equivalent, vs gallic acid: 28.08 mM Fe2+ equivalent) and

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hydroxyl radical (percentage of radical scavenging: 23.02, 81.43, 69.66 and 23.77%, respectively vs gallic acid: 100%) inhibition assays [16] (Table 5).

The presence of several classes of compounds, such as flavonoids, phenolic compounds, and terpenoids, contributes to the antioxidant activity of medicinal plants, including *Irvingia* plants. The ability of most of these compounds to interact with reactive oxygen species (ROS) by scavenging or reducing them can characterize their mechanism of action. Controlling the rates of formation and removal of ROS is a dually essential function. In fact, the intracellular levels of ROS required to perform biological functions should be secured and exceeding ROS levels that reach cytotoxic concentrations should be prevented. For example, flavonoids can exert antioxidant activity by direct radical scavenging, by interacting with the activity of a number of enzymes, including nitric oxide synthase and xanthine oxidase [56]. It has also been reported that some flavonoids (which are converted into pro-oxidants during the oxidation process) exert their antioxidant activity indirectly through Nrf2 activation [57, 58]. The ability or potency of phenolic compounds to have antioxidant functions is dictated by their structure, especially the benzene ring and the number and position of OH groups. The benzene ring is responsible for the stabilization of antioxidant molecules upon reaction with free radicals. Moreover, phenolic antioxidants can provide an H-atom to the free radical substrate to produce a non-radical substrate (RH, ROH, or ROOH) species (hydrogen atom transfer), can transfer a single electron, sequential proton loss electron transfer or can play a role in transition metal chelation [59]. The antioxidant mechanism of action has been attributed to three factors, including hydrogen transfer, quenching of singlet oxygen, or/and electron transfer [60].

Table 5. Antioxidant effects of extracts and compounds from plants of the genus *Irvingia*.

Irvingia spp.	Extracts/ Compounds	Model of the study	Significant results	Toxicity/ Cytotoxicity	Type of screening	Reference
Irvingia gabonensis	Hexane extract of the seeds	*In vitro* free radical scavenging tests (ORAC, and TEAC).	-FRAP: 283.91 mg/g; -Total Antioxidant Capacity: 431.58 mg/g.	NS	Oxygen radical antioxidant capacity (ORAC) test/ Trolox equivalent antioxidant capacity (TEAC) test	[53]
Irvingia gabonensis	Methanol extract of the seeds	*In vitro* DPPH free radical inhibition	IC_{50}: 177.22 µg/ml	NS	Colorimetric method	[54]
Irvingia gabonensis	Methyl 2-[2-formyl-5-(hydroxymethyl)-1H-pyrrol-1-yl]-propanoate (**34**); 4-[formyl-5-(methoxymethyl)-1H-pyrrol-1-yl]butanoic acid (**35**); and 5-hydroxy-2-pyridyl methyl ketone (**39**)	*In vitro* test	ED_{50}: 16.7, 11.9, >20 µM for compounds **34, 35** and **39**, respectively vs quercetin (1.3 µM)	NS	Hydroxyl Radical-Scavenging assay	[32]
Irvingia gabonensis Baill	Methanol extract of the seeds	Hypoxanthine/xanthine oxidase and 2-deoxyguanosine assays as models	IC_{50}: 28 and 281 µl in hypoxanthine/xanthine oxidase assay and 2-deoxyguanosnine tests, respectively.	NS	Hypoxanthine/xanthine oxidase assay and 2-deoxyguanosine assay models	[30]
Irvingia gabonensis	Ethanol extract of the leaves	-*In vitro* (nitric oxide and hydrogen peroxide scavenging properties) -*In vivo*; modulation of the arsenic-induced hepatic oxidative stress in albinos Wistar rats	-Nitric oxide test: IC_{50}: 258.47 µg/ml vs ascorbic acid (91.95 µg/ml) -Hydrogen peroxide scavenging: IC_{50}: 640.05 µg/ml vs ascorbic acid (109.72 µg/ml); -*In vivo* assay: decrease in serum ALT, ALP and GGT activities, CAT and MDA concentrations; increase in SOD and GPx concentrations	NS	*Colorimetric methods and Enzyme-linked Immunosorbent assays; *TECO diagnostic assay kits (Anahaema, USA)	[21]
Irvingia gabonensis	Phenolic-rich extract from the stem bark	*In vitro*: anti-oxidant activity (FRAP, DPPH, ABTS tests)	IC_{50} (µg/ml): 113.10, 18.98, and 18.25 in FRAP, DPPH, and ABTS assays, respectively.	NS	Colorimetric methods	[33]
Irvingia gabonensis	Methanol and ethanol extracts and phenol-rich extract from the seeds	*In vitro* antioxidant assays;	**-FRAP:** 0.18, 0.18, and 0.09 mM Fe2+/g, for the extracts, respectively; **-TEAC:** 3597.11, 3046.60, and 21.38 mM Trolox/g), for the extracts, respectively; -DPPH: EC_{50}: 2.81, 2.81 mg/ml, for methanol and ethanol extracts, respectively.	NS	FRAP, TEAC, and DPPH assays.	[55]
Irvingia gabonensis	Aqueous, ethanol, chloroform, and n-hexane extracts from the leaves	*In vitro* antioxidant tests (DPPH, FRAP, OH^-)	-DPPH: IC_{50}: 30.74, 21.42, 36.62, and 31.41 µg/ml for the extracts, respectively vs butylated hydroxytoluene (21.73 µg/ml); -FRAP: 23.91, 22.25, 22.43, and 11.57 mM Fe2+ equivalent for the extracts, respectively vs gallic acid: 28.08 mM Fe2+ equivalent; -Percentage of inhibition of OH^- radicals: 23.02, 81.43, 69.66, and 23.77% for the extracts, respectively vs gallic acid (100%).	NS	Colorimetric methods for DPPH, FRAP and OH^- radical scavenging tests, respectively	[16]

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5.4. Antidiabetic activity

To evaluate the antidiabetic activity of aqueous, ethanol, chloroform, and n-hexane extracts from Irvingia gabonensis leaves, Atanu et al. [16] performed α-amylase and α-glucosidase inhibition tests. In the α-amylase test, aqueous, ethanol, chloroform, and n-hexane extracts inhibited the tested enzyme with IC50 values of 30, 45, 130 and 75 µg/ml, respectively, vs acarbose (IC50 value: 55 µg/ml). Moreover, these extracts afforded IC50 values of 10, 15, 18, and 60 µg/ml (vs acarbose: 35 µg/ml), respectively, in the α-glucosidase inhibition test. In another study, the antidiabetic activity of terminalin (45), a phe-nolic compound isolated from the aqueous extract of Irvingia gabo-nensis seeds was evaluated through inhibition of protein tyrosine phosphate enzymes (PTPs). As a result, terminalin (45) inhibited more than 80% of the catalytic activity of PTPN1, PTPN9, PTPN11 and PTPRS in vitro leading to a significant increase in glucose uptake in differentiated C2C12 muscle cells, indicating that this compound exhibits antidiabetic effects through the PTP inhibitory mechanism [34].

5.5. Other biological activities

In an in vitro study, Chung et al. [61] demonstrated the inhibitory ef-fect of the methanol leaf extract of Irvingia malayana on the human receptor 5HT1a with an inhibition rate of 65%, inferring that this ex-tract can overcome disorders of the central nervous system, such as migraine, sleeping disorders, Alzheimer's disease, epilepsy, and the Parkinson's disease [61]. Two fractions prepared from the methanol extract of Irvingia malayana inhibited the growth of the human leu-kemia cell-line HL60 by 73.9 % and 46.3 %, respectively [62]. Ng et al. [63] used the rat aortic ring assay to screen the antiangiogenic ac-tivity of the methanol extract of Irvingia malayana and its isolate bet-ulinic acid. At 100 µg/ml, both the extract and butilinic acid inhibit-ed human umbilical vein endothelial cells by 46.5 and 45.5%, respec-tively, vs suramin (percent inhibition: 55.5%). Furthermore, the studied extract revealed no cytotoxic activity against HepG2, HCT- 116, T-47D, NCI-H23 and CCD-18Co cells, as the IC50 values were 88.23, 54.94, 64.32, 78.12 and 111.34 µg/ml, respectively [63]. In a randomized clinical trial, Méndez-Del Villar et al. [64] described the effect of I. gabonensis administration in reverting metabolic syn-drome (7 patients out of 12 patients; 58.3%) compared with the group of patients who received placebo (2 patients remitted out of 12 patients; 16.7%). These results attested to the effectiveness of Irvingia against metabolic diseases, such as diabetes [64]. The ethanol extract of I. gabonensis leaves inhibited the growth of the worm Heligmoso-moides bakeri with percent inhibition values of 71.43, 57.14 and 42.9% at concentrations of 500, 250 and 125 mg/ml, respectively, suggesting that I. gabonensis extract possesses anthelminthic activity [65]. To evaluate the protective role of Irvingia gabonensis, the ethanol extract of I. gabonensis leaves (at 250 and 500 mg/kg) was administered to male Wistar rats with sodium arsenite (2.5 mg/kg)-induced toxicity. This extract decreased the activities of ALT (52.71, 57.24, 40.72 and 39.65 U/l), AST (9, 9.46, 9.23 and 8.92 U/l) and γGT (5.21, 3.47, 6.94 and 4.63 U/l), respectively when compared to the group treated only with sodium arsenite [ALT (78.61 U/l), AST (22.99 U/l) and γGT (10.42 U/l)] [4]. Recently, Ugwu et al. [66] used carrageenan-induced edema to evaluate the anti-inflammatory activity of solid lipid mi-croparticles prepared from unPEGylated lipid matrices of Irvingia fat matrix. Irvingia-loaded microparticles significantly reduced the volume of edema in rats by 38, 40, 87, 65 and 67% after 0.5, 1, 2, 3 and 4 h, respectively [66] (Table 6).

Table 6. Other pharmacological activities of extracts and compounds from *Irvingia* plants.

Irvingia spp.	Extracts/ Compounds	Model of the study	Significant results	Toxicity/ Cytotoxicity	Type of screening	Reference
Irvingia gabonensis	Water and ethanol extract prepared from the stem bark	Male mice	-Reduction of the locomotion in mice treated with water extract (250-750 mg/kg); -Production of time- and dose-related analgesia by both extracts (250-750 mg/kg).	NS	Hot plate test	[67]
Irvingia gabonensis	Aqueous extract of leaves	-Gastrointestinal motility test in mice, and; -Castor oil-induced diarrhea in mice.	*Decrease in the gastrointestinal motility: 40.12, 39.45 and 37.45 % at the doses of 100, 200 and 400 mg/kg, respectively; *Protection of mice by 71.43, 81.63, 83.27% at 100, 200 and 400 mg/kg of extract, respectively.	NS	-Gastrointestinal motility test in mice, and; -Castor oil-induced diarrhea in mice.	[11]
Irvingia gabonensis	Ethanol (80%) extract prepared from the leaves.	Model: The worm *Heligmosomoides bakeri*	Percentage of larvae death: 71.43, 57.14 and 42.9% of larval deaths at the concentrations of 500, 250, and 125 mg/ml, respectively.	NS	Cell viability	[65]
Irvingia gabonensis	Ethanol (50%) extract from the leaves.	Sodium arsenite-induced hepatotoxicity in male Wistar albino rats	Decrease in the activity of serum biochemical parameters: -ALT: 52.71, 57.24, 40.72 and 39.65 U/l; respectively; -AST : 9, 9.46, 9.23 and 8.92 U/l; respectively; -γGT: 5.21, 3.47, 6.94 and 4.63 U/l, respectively when compared with the group treated with sodium arsenite alone [ALT (78.61 U/l), AST (22.99 U/l), and γGT (10.42 U/l)].	NS	Sodium arsenite-induced hepatotoxicity in male Wistar albino rats	[4]
Irvingia gabonensis	Aqueous, methanol and hexane extracts from the leaves.	*In vivo* anti-diarrheal activity in rat models	Percentage of protection: -Aqueous extract: 80% at 100 and 200 mg/kg, vs loperamide (80% at 2 mg/kg) -Methanol extract: 80% protection at 200 mg/kg, vs loperamide (80% at 2 mg/kg); -Hexane extract: 40 and 60% protection at 100 and 200 mg/kg, respectively.	NS	NS	[46]
Irvingia wombolu	Solid lipid microparticles prepared from unPEGylated lipid matrices of *Irvingia* fat matrix (*Irvingia*-loaded microparticles)	Rat paw edema model	Reduction of the volume of edema in rats in percentages: 38, 40, 87, 65 and 67% after 0.5, 1, 2, 3 and 4h, respectively	NS	Carrageenan rat paw edema test	[66]
Irvingia gabonensis	Aqueous, ethanol, chloroform, and n-hexane extracts from the leaves	*In vitro* antidiabetic test using α-amylase and α-glucosidase inhibition tests	*α-amylase test: IC_{50}: 30, 45, 130 and 75 µg/ml, respectively, vs acarbose (IC_{50}: 55 µg/ml); * α-glucosidase inhibition test: IC_{50}: 10, 15, 18, and 60 µg/ml, respectively (vs acarbose: 35 µg/ml)	NS	α-amylase and α-glucosidase inhibition tests	[16]

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6. Toxicity profile of *Irvingia* spp.

A number of studies have reported on the toxicity profile of plants from the genus *Irvingia*. For example, in a study published by Kothari et al. [68], the oral administration of *Irvingia gabonensis* extract at 0, 100, 1000 and 2500 mg/kg for 90 days did not induce any clinical signs or mortality in Sprague Dawley rats. Moreover, no treatment-related changes in clinical signs, functional observations, mortality, body weight, weight gain or feed consumption were noted. Similarly, hematological, clinical chemistry, urine analysis parameters and organ weights did not reveal any toxicologically significant treatment-related changes [68]. Furthermore, the subchronic oral administration of the aqueous leaf and stem bark extracts of *I. gabonensis* in male albino Wistar rats at 1000 and 2000 mg/kg did not induce any significant changes compared to the control group that did not receive any treatment. In brief, the oral administration of three doses (100, 1000 and 2000 mg/kg) of aqueous leaf extract of *I. gabonensis* did not affect serum biochemical markers of toxicity, such as ALT (63.30, 59.50 and 58.00 IU/L at 100, 1000 and 2000 mg/kg, respectively, vs untreated control: 66.50 IU/L), AST (158.33, 159.33, and 158.00 IU/L at 100, 1000 and 2000 mg/kg, respectively, vs untreated control, 159.16 IU/L) and ALP (127.90, 102.00 and 121.13 IU/L at 100, 1000 and 2000 mg/kg, respectively, vs untreated control, 103.50 IU/L), suggesting that these extracts might not affect liver physiology [69].

To evaluate the potential of ethanol extract from *Irvingia gabonensis* seeds in reverting the cardiotoxicity caused by doxorubicin in mice, Olorundare et al. [15] administered 100, 200 and 400 mg/kg to doxorubicin (15 mg/kg)-mediated cardiotoxicity and determined the level of serum cardiac enzymes, such as cardiac troponin I (cTI) and lactate dehydrogenase (LDH), and cardiac tissue oxidative stress markers [catalase (CAT), malonyldialdehyde (MDA), superoxide dismutase (SOD), glutathione-S-transferase (GST), glutathione peroxidase (GSH-Px) and reduced glutathione (GSH)]. The plant extract increased the levels of serum GSH [21.3, 17.0, 19.6 and 24.7 U/L at 20, 100, 200, and 400 mg/kg, respectively vs Dox-treated group (14.8 U/L) and negative control (18.8 U/L)], GST [2.6, 2.0, 2.4, and 3.0 U/L at 20, 100, 200 and 400 mg/kg, respectively vs Dox-treated group (1.1 U/L) and negative control (1.6 U/L)], GPx [2.4, 1.3, 2.3 and 3.3 U/L at 20, 100, 200, 400 mg/kg, respectively vs Dox-treated group (1.0 U/L) and negative control (1.2 U/L)], SOD [11.5, 11.1, 12.8 and 15.4 at 20, 100, 200 and 400 mg/kg, respectively vs Dox-treated group (6.9 U/L) and negative control (9.5 U/L)], and CAT [51.4, 54.2, 56.6 and 78.7 U/L at 20, 100, 200, 400 mg/kg, respectively vs Dox-treated group (16.7 U/L) and negative control (43.6 U/L)]. In contrast, there was a decrease in the levels of MDA [5.2, 5.3, 3.9 and 3.5 U/L at 20, 100, 200 and 400 mg/kg, respectively vs DOX-treated group (12.8 U/L) and negative control (4.3 U/L)] [15].

7. Critical assessment and discussion

The present work discusses recent developments in the traditional uses, phytochemical composition, and pharmacological and toxicological studies of plants from the genus *Irvingia*. Research gaps that have not been explored thus far are also presented and discussed.

At least 6 species (*Irvingia gabonensis*, *I. grandifolia*, *I. tenuinucleata*, *I. malayana*, *I. wombolu* and *I. midbr*, among others) of *Irvingia* are traditionally used to relieve a number of diseases, including diarrhea, scabies, toothache, yellow fever, inflammation, liver and gastrointestinal disorders, and others. In traditional medicine, the fruit, bark, leaves, seeds and roots are the most commonly used organs of *Irvingia* plants. The decoction is the main mode of preparation, while the main mode of administration is by the oral route. Except for betulinic acid (**2**), which was also pinpointed to originate from *Irvingia malayana*, the remaining compounds were identified from various organs [stem bark (compounds **1**-**6**, [27]), seeds (compounds **7**, **9** and **10**, [30]; compounds **4** and **9**, **10**-**33**, [31]; compounds **34**-**41**, [32]) of *Irvingia gabonensis*. Most importantly, these compounds were found to exhibit antimicrobial (compounds **1**-**6**, [27]) and antioxidant (compounds **34**, **35** and **39**, [32]) activities. Nevertheless, a substantial amount of extracts were prepared from *Irvingia* plants and evaluated for a number of biological activities, including antiprotozoal, antimicrobial, antioxidant, antidiabetic, antiangiogenic, and anthelmintic activities.

In antiprotozoal assays, three plant species were involved, including *Irvingia gabonensis* (antiplasmodial and anti-*Trypanosoma brucei;* IC_{50}: <8 µg/ml), *Irvingia malayana* (antiplasmodial) and *Irvingia grandifolia* (antileishmanial activity; IC_{50} values: <8.4 µg/ml), whereas the solvents mostly used for extraction comprised ethanol, methanol and dichloromethane. Stem bark and leaves were the plant organs tested. As already discussed, the seeds of *Irvingia* spp. contain a number of secondary metabolites (compounds **10**-**41**) that can be further isolated and characterized as antiprotozoal compounds. In most reported studies, the cytotoxicity of plant extracts was not investigated against human mammalian cells. The antiprotozoal mechanisms of action of extracts and compounds from *Irvingia* spp. are still unexplored. Thus, research breaches to be filled in antiprotozoal drug screening include the following: (i) antiprotozoal guided-fractionation of constituents from all known and available species (>5) of *Irvingia* should be performed; (ii) antiprotozoal experiments should be followed by cytotoxicity assays to depict the selectivity of test samples; (iii) the polarity of solvent used for extraction should be varied to extract both polar and nonpolar potential antiprotozoal compounds from *Irvingia* spp.; (iv) appropriate negative and positive controls should be considered in antiprotozoal assays; and (v) in-depth toxicity studies and antiprotozoal mechanisms of action of the most promising compounds should be explored. In antimicrobial assays, numerous reports related to the screening of plant extracts are widespread across the literature; however, only a few authors [27] have isolated and characterized antimicrobial compounds from *Irvingia gabonensis*. Therefore, it will be of interest for researchers working on antimicrobial drug discovery, to (i) explore other *Irvingia* species and their constituents with respect to antimicrobial drug screening, (ii) screen extracts and compounds against dermatophytes (Epidermophyton, *Microsporum*, and *Trichophyton* spp.) and associated fungi that cause superficial infections of the skin, hair and nails, and (iii) perform toxicity studies and antimicrobial mechanisms of action of the most promising compounds.

Although several methods (FRAP, DPPH and NO scavenging tests, etc.) have been used to screen extracts and compounds from *Irvingia* plants, only *Irvingia gabonensis* was the plant species that was mostly involved in biological tests. Although the presence of polyphenols in plants, in general, has explained the antioxidant nature of plants [70, 71], the use of several approaches to study the anti-radical scavenging activity might influence the outcome of the tests. On the other hand, studying the antioxidant activity of plants and their secondary metabolites might help to better elucidate the mechanisms of action of bioactive extracts or compounds. In the case of *Irvingia*, a study of the antioxidant activity of other *Irvingia* species (such as *Irvingia malayana* and *Irvingia grandifolia*) and compounds thereof is warranted. A couple of antidiabetic experiments were recently conducted by Atanu et al. [16] and Yoon et al. [34] using enzyme inhibition assays (inhibition of α-amylase, α-glucosidase and protein tyrosine phosphatase). However, these experiments provide an idea about the *in vitro* antidiabetic effect of only one species of *Irvingia*, i.e. *Irvingia gabonensis*. Extending antidiabetic studies to other *Irvingia* species might afford more insights into the antidiabetic potential of *Irvingia* spp. and their secondary metabolites. Other biological tests on extracts and compounds from *Irvingia* spp. included antiangiogenic (isolate of *I. malayana*: betulinic acid; [63]), anthelmintic (ethanol extract of *I. gabonensis* leaves; *Heligmosomoides bakeri*; percent inhibition: 42.9% at 125 mg/ml; [65], and hepatoprotective (sodium arsenite-induced toxicity in male Wistar rats; decrease in ALT and AST enzymes; *I. gabonensis*; [4]) activities. However, there is almost no information about the secondary metabolites (active principles) that are responsible for the observed biological activities. As *Irvingia gabonensis* is the most investigated plant of the genus *Irvingia*, phytochemical and biological studies of the other species (>5) of *Irvingia* are warranted. Overall, the genus Irvingia comprises at least 6 species (*Irvingia gabonensis*, *I. grandifolia*, *I. tenuinucleata*, *I. malayana*, *I. wombolu* and *I. midbr*) with ethnomedicinal indications. Various organs (leaves, stem bark, seeds, among others) of these species are used traditionally to overcome a number of diseases, such as diarrhea, yellow fever, scabies, toothache, inflammation, dysentery, liver and gastrointestinal disorders.

Modern pharmacological studies revealed antiprotozoal, antimicrobial, antidiabetic, antioxidant, anti-inflammatory and hepatoprotective activities, thus validating the ethnomedicinal uses of *Irvingia* plants in the treatment of fever and inflammation conditions and bacterial gastroenteritis (vomiting, diarrhea). Furthermore, several studies revealed the presence of more than

40 compounds from *Irvingia* plants, mostly phenolic compounds, flavonoids, and terpenoids. These compounds might be responsible for the reported biological activities of *Irvingia* plants. Nevertheless, there are research gaps that need to be filled regarding the potential application of *Irvingia* spp., from their ethnopharmacological validation and phytochemical evaluation to preclinical and clinical investigations. These include: (i) lack of *in vitro* and *in vivo* toxicity tests, and mechanistic studies on extracts and compounds from *Irvingia* spp. in reported works, (ii) lack of appropriate controls in most the experiments, (iii) only a few of the existing species of *Irvingia* have been studied till date and most of the traditional indications (jaundice and related symptoms, scabies, asthenia or respiratory ailments, and so on) have not been scrutinized using modern pharmacological experiments; (iv) Compared to *Irvingia* crude extracts, less information is available regarding biological studies of pure compounds from *Irvingia*. Therefore, (a) more studies on *in vitro* and *in vivo* toxicity tests, as well as mechanistic studies of extracts and compounds from *Irvingia* spp., should be investigated; (b) robust and comprehensive phytochemical analyses, such as LC-MS/MS, GC/MS, HPTLC, and UHPLC-ESI-Q-TOF-MS, in association with biological screening (bioassay-guided) should be performed to substantially identify the bioactive compounds from *Irvingia* species; and (c) other *Irvingia* species and traditional indications should be considered in modern pharmacological studies. These studies might contribute to the potential therapeutic applications of *Irvingia* in the treatment of various diseases.

8. Conclusions and perspectives

The present study provides a comprehensive analysis regarding traditional uses, phytochemical analyses, and pharmacological and toxicity studies of plants from the genus *Irvingia*. *Irvingia* plants are used for the traditional treatment of a number of diseases, such as diarrhea, yellow fever, scabies, toothache, inflammation, dysentery, and liver and gastrointestinal disorders. Previous reports have revealed a number of pharmacological activities, including antiprotozoal, antimicrobial, antidiabetic, antioxidant, anti-inflammatory and hepatoprotective activities. The reported activities have been attributed to the existence of a number of secondary metabolites (flavonoids, phenolic compounds, terpenoids, tannins, saponins, alkaloids, etc.) in *Irvingia* plants. Nevertheless, a number of studies (*in vitro* and *in vivo* toxicity and in-depth mechanistic experiments, additional phytochemical and pharmacological studies of the uninvestigated species of *Irvingia*) are needed for the successful utilization of *Irvingia* plants in the treatment of various diseases.

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