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PRENYLATED BENZOIC ACID DERIVATIVES FROM *PIPER SPECIES* AS SOURCE OF ANTI-INFECTIVE AGENTS

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ABSTRACT

A number of prenylated benzoic acids derivatives with interesting biological activities have been previously isolated and characterized from different species of piperaceae family. Several *Piper species* contained structurally similar compounds with diverse biological activities such as anti-bacterial, anti-fungal, insecticidal as well as anti-parasitic all of which produces compounds that can be classified as prenylated benzoic acid derivatives. *Piper* sp has proven to serve as a source of potential anti-infective agents by developing a biosynthetic route to the synthesis of prenylated benzoic acids derivative natural products as their chemical defense system. Despite the frequent isolation of these interesting compounds with strong biological activity, yet none have been taking into consideration for development into therapeutic agents.

INTRODUCTION: Medicinal plants are important sources of natural compounds with novel potential therapeutic agents [1, 2]. Plants are rich in a wide variety of secondary metabolites such as tannins, terpenoids, alkaloids and flavonoids [3] and they have limitless ability to synthesis aromatics most of which are phenols.

Medicinal plants are used for centuries as remedies for human diseases and offer the richest biosources of drugs or traditional medical system, modern medicines, neutraceuticals, food supplements, folk medicines, pharmaceuticals, intermediate and chemical entities for synthetic drugs [4]. Among the estimated 250,000-500,000 plant species [5], *Piper species* are estimated to contained 4000 species [6] widely distributed in the world. About 25 to 50% of current pharmaceuticals are derived from plants [3]; none of the *Piper species* are yet to be developed into therapeutic agent.

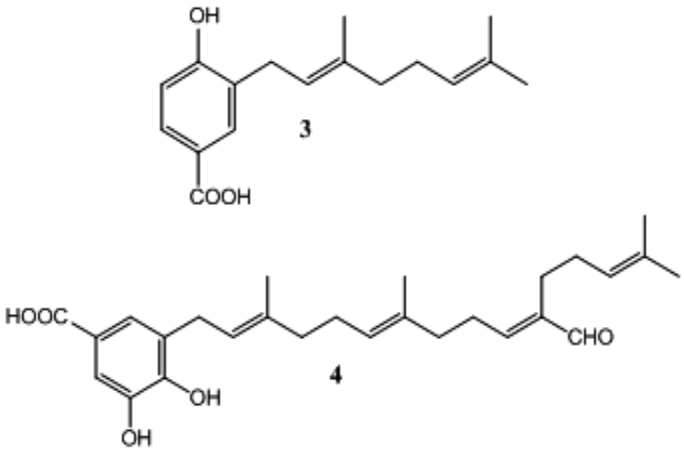
Piper is one of the species found in ancient Ayurvedic medicine not only used as spices but also as folk medicine [6]. Piperaceae family is a basal angiosperm family, estimated to contained more than 4000 species widely distributed in the tropical and subtropical region of the world, its species are chemically very rich and contained major classes of compounds [7, 8], of which among them includes benzoic acid derivatives.

This review paper tend to highlight some of the recent bio-activity guided isolation and characterization of prenylated benzoic acid derivatives that have been previously reported from different *Piper* species with different interesting biological activities.

Prenylated benzoic acid derivatives from *P. species*: Several phytochemical investigation on piper family has been investigated to contain several interesting prenylated benzoic acid with interesting biological activities and also have been described to contained structurally similar compounds [9] exhibiting diverse

biological activities such as antibacterial [10, 11, 12], antifungal [13, 14, 15, 16], insecticidal [17] and antiparasitic [10, 18, 19] all of which produces compounds that can be classified as prenylated benzoic acid derivatives, and more related compounds are continuously to be isolated with potent biological activities.

Phytochemical investigations carries out on deferent *Piper* species [14] has revealed the isolation of several related prenylated benzoic acid derivatives. 3-[(2E, 6E, 10E)-11-carboxy-3, 7, 15-trimethyl-2, 6, 10, 14-hexadeca-tetraenyl)-4, 5-dihydroxybenzoic acid **7**,3-[(2E, 6E, 10E)-11-carboxy-13-hydroxy-3, 7, 15-trimethyl-2, 6, 10, 14-hexadecatetraenyl]-4, 5-dihydr oxybenzoic acid **8** and 3-[(2E, 6E, 10E)-11-carboxy-14-hydroxy-3, 7, 15-tri-methyl-2, 6, 10, 15-hexadeca tetraenyl]-4, 5-dihydroxy benzoic acid **9** are acyclic diterpene dihydroxybenzoic acids recently reported to be isolated from *Piper heterophyllum* and *P. aduncum* along with 4, 5- dihydroxy-3-(E, E, E-11-formyl-3, 7, 15-trimethyl-hexadeca-2, 6, 10, 14-tetraenyl) benzoic acid (arieianal) **3**, 3, 4-dihydroxy-5-(E, E, E-3, 7, 11, 15-tetramethyl-hexadeca-2, 6, 10, 14-tetraenyl)benzoic acid **4**, 3-(E, E, E-3, 7, 11, 15-tetramethyl-hexadeca-2, 6, 10, 14-tetraenyl)benzoic acid **10**, 3-(3, 7-dimethyl-2, 6-octadienyl)-4-methoxy-benzoic acid **11**, 4-hydroxy-3-(3, 7-dimethyl-2,6-octadienyl)benzoic acid **19** and 4-hydroxy-3-(3-methyl-1-oxo-2-butenyl)-5-(3-methyl-2-butenyl)benzoic acid **30** with antiparasitic activity. Compound **4**, **10** and **11** are acyclic diterpene dihydroxybenzoic acids, **3** and **19** are geranylated *p*-hydroxybenzoic acids and geranylated *p*-methoxybenzoic acid respectively, while compound **30** is a di-prenylated *p*-methoxybenzoic acid.



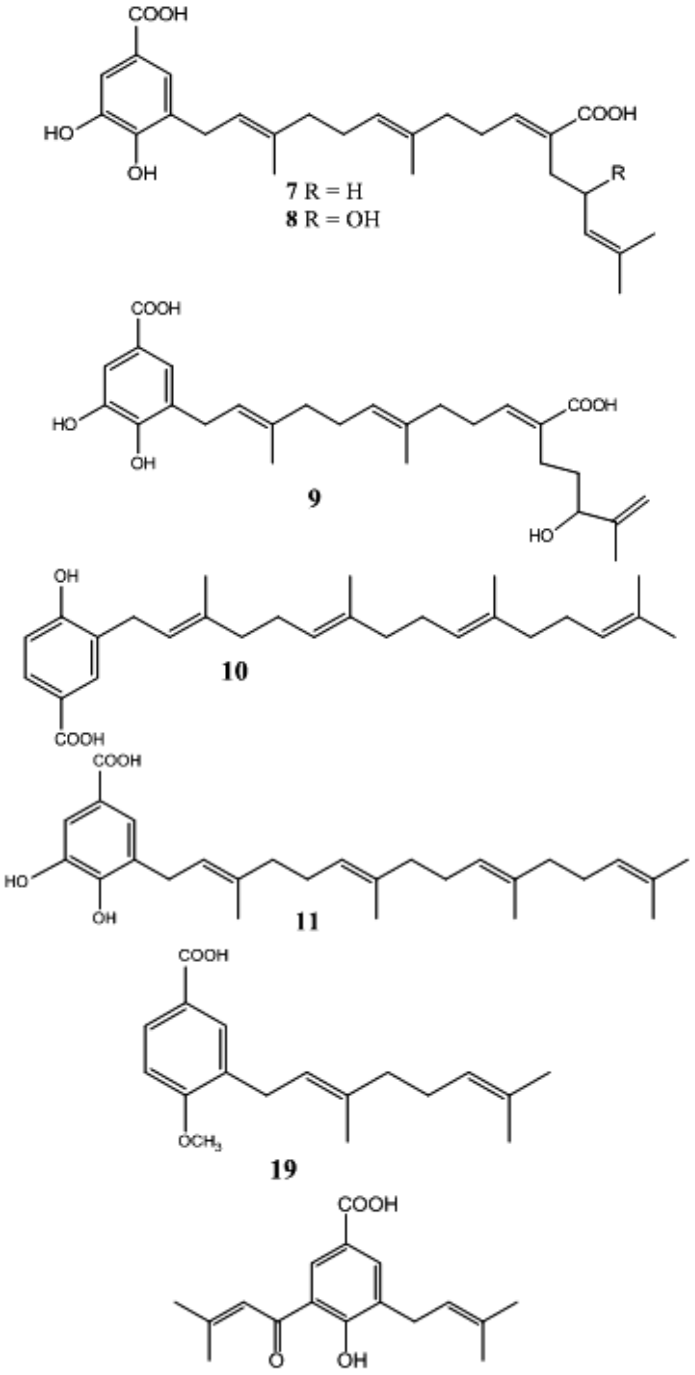


FIGURE 1

The leaves of *Piper aduncum* are traditionally used for the treatment of inflammation and as antiseptic [10]. These compounds shown to have potent antiparasitic against *Leishmania braziliensis*, *Trypanosoma* cruzi and *Plasmodium falciparum* with **19** having potent selective activity against *L. brazilianses* at IC_{50} 6.5 µg/ml while **11** and **7** exhibit moderate antiplasmodial and trypanocidal activities at IC_{50} 3.2 µg/ml and IC_{50} 16.5 µg/ml respectively [19].

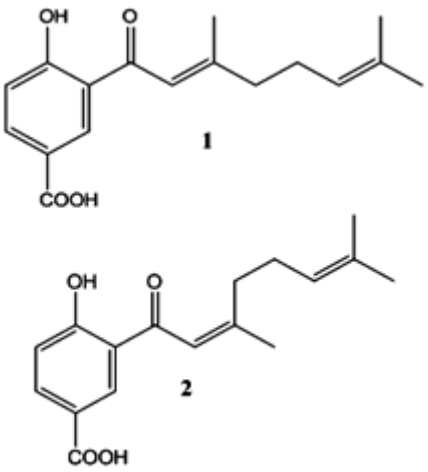


FIGURE 2

4-hydroxy-(3',7'-dimethyl-1'-oxo-octa-E-2'-6'-dienyl) benzoic acid **1**, **3** and 4-hydroxy-(3',7'-dimethyl-1'-oxo-octa-2'-Z-6'-dienyl) benzoic acid **2** are geranylated *p*-hydroxybenzoic acids and acyclic diterpene dihydroxybenzoic acids first reported to be isolated from *Piper murrayanum* (**fig. 2**). The *P. murrayanum* is ethnomedicinally used by Jamaican for the treatment of fever, pain, wounds, toothache, colds, asthma, stomach ache and insect repellant [20, 21] while **10** and **11** were reported from *Piper saltuum* [22].

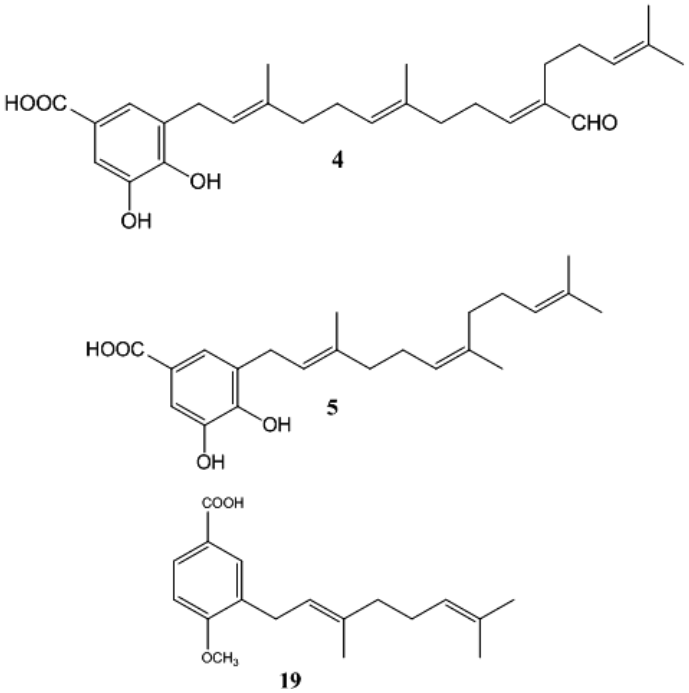


FIGURE 3

Compound **4**, piperoic acid **5** and **19** were reported from *Piper arieianum* and *Piper aduncum* used locally as ant-repellant and for both treatment of stomach ache and as an insect repellant, respectively [11, 21].

Bio-activity guided fractionation on different *P*. species has revealed the isolation of antiparasitic prenylated benzoic acid derivatives lanceaefolic acid methyl ester [methyl ester of 4, 5- dihydroxy-3-(3-methyl-2-butenoyl)benzoic acid] **12**, 4, 5- dihydroxy-3-(3-methyl-2-butenoyl)benzoic acid **13**, methyl 4-hydroxy-3-(methyl-2- butenyl)benzoate **17**, methyl 4-hydroxy-3-(20 -hydroperoxy-30 -methyl-30 -butenyl)benzoate **18**, and 3, 4-dihydroxy-5-(2-hydroxy-3-methyl-3-butenyl) benzoate **20**, 4-hydroxy-3-(2-hydroxy-3-methyl-3-butenyl)benzoate **21**, methyl 3, 4-dihydroxy-5-(3-methyl-2-butenyl)benzoate **22**, 4-hydroxy-3, 5-bis(3-methyl-2-butenyl)benzoic acid **23**, 4-methoxy-3,5-bis(3-methyl-2-butenyl)benzoic acid **24**, 4-hydroxy-3-(2-hydroxy-3-methyl-3-butenyl)-5-(3-methyl-2-butenyl) benzoic acid **25**, 3-(2-hydroxy-3-methyl-3-butenyl)-4-methoxy-5-(3-methyl-2-butenyl)benzoic acid **26**, 3-[(1E)-3-hydroxy-3-methyl-1-butenyl)-4-methoxy-5-(3-methyl-2- butenyl)benzoic acid **27**, 4-hydroxy-3,5-bis(2-hydroxy-3-methyl-3- butenyl)benzoic acid **28**, 4-Hydroxy-3-(3 -methyl-2-butenyl)benzoic acid **29** are di-prenylated *p*-methoxybenzoic acid, mono-prenylated dihydroxybenzoate esters, mono-prenylated dihydroxy benzoic acids, mono-prenylated *p*-hydroxybenzoate esters and mono-prenylated *p*-hydroxybenzoic acids, respectively has also being reported to be isolated and characterized from *Piper lanceaefolium* [13], *P. aduncum* [15, 16], *P. hostmannianum* [15, 16], *P. glabratum* and *P. acutifolium* [18] (**fig. 4**).

Compound **12** was reported to exhibit antifungal properties showing inhibition (MIC 100µg/ml) against *Candida albicans* [13] while **18** was recently shown to displayed antifungal activity (MIC 5.0 µg) against both *Cladosporium cladosporioides* and *C. sphacrospermum* [16].

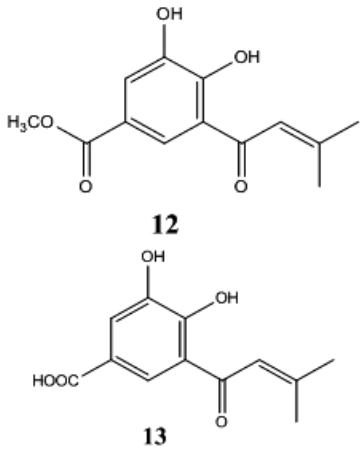
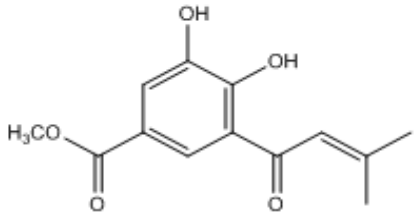


FIGURE 4



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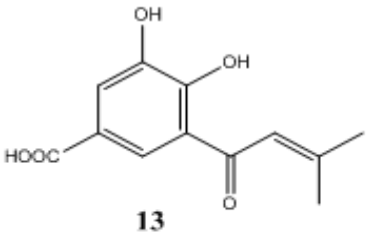

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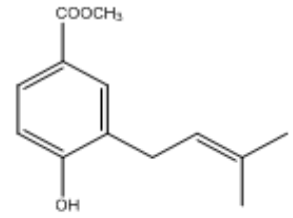

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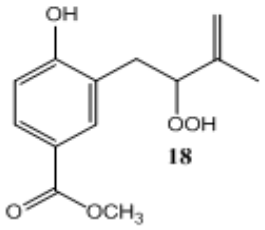

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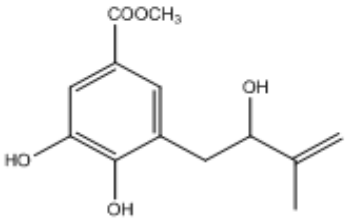

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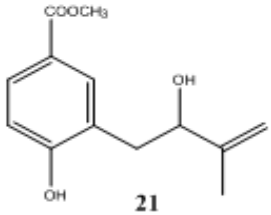

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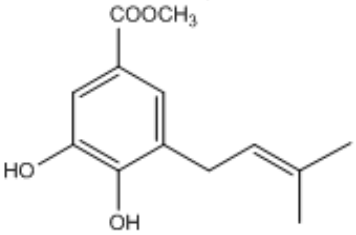

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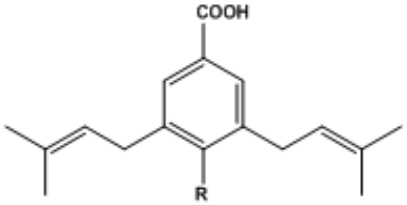
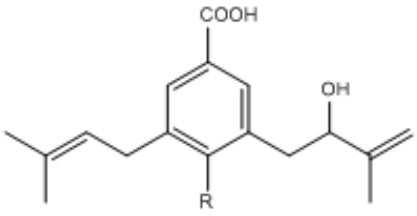
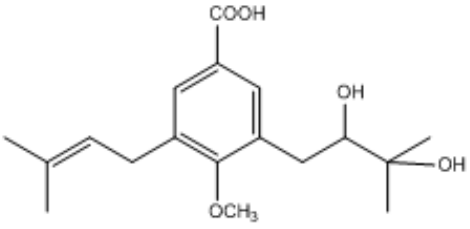


23 R=OH
24 R=OMe



25 R=OH
26 R=OMe



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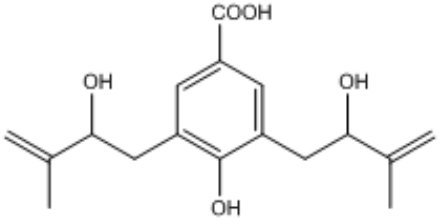

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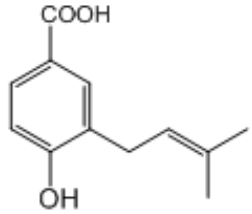

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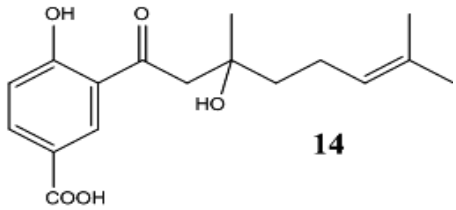
FIGURE 5

The antiparasitic **22** exhibit both *leishmanicicidal* activity (IC_{50} 18.2, 13.8 and 18.5µg/ml) against *Leishmania amazonensis, L. brazilliensis* and *L. donovani*, respectively. The *trypanocidal* activity of **22** also reported to have activity (18.5µg/ml) against *T. cruzi*. **20** and **21** has significant trypanocidal activity at IC_{50} 16.4 and 15.5µg/ml while **17**; **24**-**28** has shown poor or no effective against parasite [18]. *Piper. Guanacastensis* has also been reported to contained compound **17** and **29** while compound **17** is biologically active (LC_{50} 20.5 µg/ml) against mosquito larvae, *Aedes atropalpus* [17].

A series of bio-activity guided fractionations leads to the isolation of fungitoxic compounds 4-hy-droxy-3-(3,7-dimethyl-3-hydroxy-1-oxo-6-octenyl)benzoic acid **14**, 4-hydroxy-3-(2, 3-dihydroxy-3-methylbutyl) benzoate **15** and 4-hydroxy-3-(2,3 -dihydroxy-3-methylbutyl)benzoate **16** from *Piper crassinervium*, *P. aduncum* and *P. hostmannianum*, respectively. These compounds (**14**, **15** and **16**) have potent activity against both *Cladosporium cladosporioides* and *C. sphaerospermum* at MIC 0.5, 5.0 and 0.5 µg, respectively [15] (**fig. 5**).



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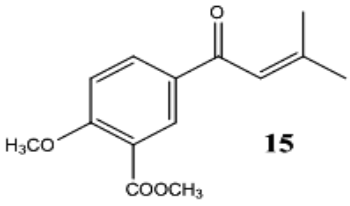

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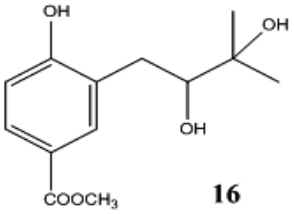

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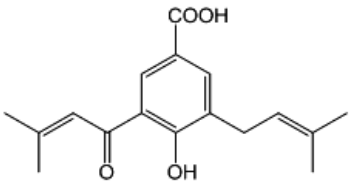
Further literature survey on biologically active benzoic acid derivative compounds from *P. species* revealed the isolation and characterization of antibacterial and mulluscidal compounds **17**, **19, 30**, **31**, **32**, 1-(1-methylethyl)-4-methyl-3-cyclohexenyl 3,5-bis(3-methyl -2-butenyl)-4-hydroxybenzoate **33** (**fig. 6**) from *Piper aduncum* traditionally used by the villagers from the coastal areas of the Morobe Province of Papua New Guinea (P.N.G.) for the treatment of wounds. Compound **17**, **30**, **31** and **32** were shown to display both mulluscidal and antibacterial activities with **30** (13 ppm), **31** (10 ppm) and **32** (15 ppm) having activity against *Biomphalaria glabrata*. Compound **17**, **30**, **31** and **32** exhibit antibacterial activity against both *Bacillus subtilis and Micricoccus luleus* at MIC 2.8, 0.9, 1.25 and 2.0 nmol respectively [10].



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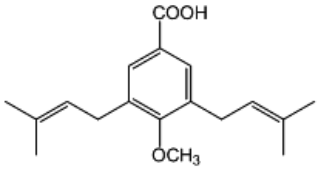

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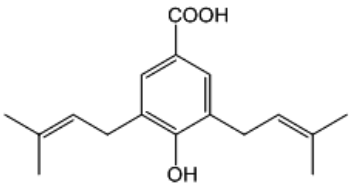

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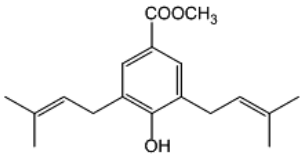

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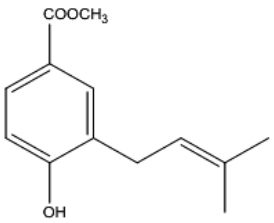

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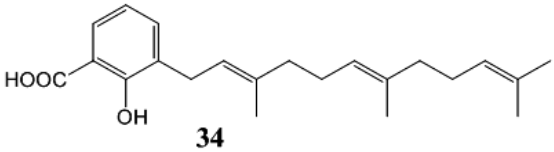

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FIGURE 6

3-Farnesyl-2-hydroxybenzoic acid (**34**) is an anti-bacterial compound isolated and characterized by Rugg, (2006) from the leaves of *Piper multiplinervium*. The plant is traditionally used by the local Kuna Indians of Panama for the treatment of stomach ache. Compound **34** was found to have broad spectrum of activity against both Gram positive and Gram negative bacteria including *Escherichia coli*, *Staphylococcus aureus* and *Helicobacter pylori*. **34** has antimicrobial activity at MICs between 2.5 and 5 µg/ml against *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa* as well as *Candida albicans* and showed anti-*Helicobacter pylori* activity at MIC 37.5 µg/ml.

Phytochemical investigation recently reported by Puhl, *et al* (2011), revealed the isolation and characterization of antimicrobial agents **1** and **2** of which belongs to the family of prenylated benzoic acid derivatives from *P. gaudichaudianum*. Compound **1** and **2** shown activity against both *S. aureus* and *B. subtilis* using bioautographic analysis [23].

CONCLUSION: Phytochemical investigations previously carried out on different *Piper* species revealed to contain several interesting prenylated benzoic acid with interesting biological activities and has also being described to contain structurally similar compounds[9, 14]. Despite the frequent isolation of these interesting compounds with strong biological activity, yet none have been taking into consideration for development into therapeutic agents.

Piper sp has proven to serve as a source of potential anti-infective agents by developing a biosynthetic route to the synthesis of natural products as their chemical defense system. These natural products posses broad spectrum of activities against most infections among them includes prenylated benzoic acid derivatives.

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