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Isodon Diterpenoids, Derivatives and their Pharmacological Potentials-A Review

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Abstract

The searches of various literatures have shown the genus *Isodon* to be a source of different compounds with interesting biological activities. The genus has provided many efficacious herbal medicines that are used in various countries including China; therefore, it has become the centre of attention to phytochemistry and pharmacology researchers. There are many reports on chemical and biological aspects of *Isodon* species, especially in China and other parts of the world; however, reports on African *Isodon* species are scanty. Since the literature indicates the genus to be rich in diterpenoids with potential therapeutic activities as revealed herein, with African species waiting to be explored, it is the responsibility of the phytochemists and pharmacologists to fill this knowledge gap. Herein, ethnomedicinal uses of some of *Isodon* plants in various traditional medicine systems, phytochemistry of the genus from 2016 to date, synthesis of *Isodon* diterpenoids and derivatives are discussed.

Keywords: *Isodon* diterpenoids; Natural Products; *Isodon* phytochemistry; Herbal Medicines; Diterpenoids synthesis

Introduction

Natural products are chemical substances that are obtained from nature (animals, plants, micro-organisms and others). These compounds are known to possess distinctive biological properties, thus play vital role in the medicinal chemistry fields. Among many classes of natural compounds, terpenoids have emerged to be one of the main groups used as either drugs or drug intermediates. Literatures have indicated majority of terpenoids to be extracted from various plant sources, and very few have been isolated from other sources such as animals and microbes (Borowitzka 1995, Martin et al. 2003, Zwenger and Basu 2008).

Isodon, a genus belonging to the family Labiatae (= Lamiaceae), is comprised of ~150 species with most of them distributed in tropical and subtropical Asia. Although the genus is reported to be endemic to China, a few species have been observed in Africa, which include *Isodon ramosissimus* and *Isodon schimperi* (Harley et al. 2004). Many plants of this genus are known for their fragrant leaves and attractive flowers; thus, it is not surprising to find them used for decoration, in flavouring and in making fragrants (Venkateshappa and Sreenath 2013). The contribution of *Isodon* species (Xihuangcao in Chinese) in traditional medicine is unquestionable, especially in Chinese traditional medicine system. Generally, in Chinese traditional medicine systems, *Isodon* plants are used for treatment of acute hepatitis, trauma, dysentery, enteritis, bacterial infections, and inflammation. They are also known for their hepatoprotective effects, and treatment of sore throats, malaria, jaundice, pneumonia, gastrointestinal disorders and cholecystitis (Lianzhu et al. 2011). In China, beverages and healthcare

foods from *Isodon* plants are widely used for refreshments as well as treating various illnesses. Recently, *Isodon* products have gained acceptance by many people in China and other parts of the world (Lianzhu et al. 2011). Owing to their effectiveness in treatments of various illnesses, the plants of this genus have been the centre of attention to researchers of various fields of science (Dilshad et al. 2008, Chen et al. 2009, Kang et al. 2010, Gu et al. 2010, Yu et al. 2014, Abbasi et al. 2019, Janbaz et al. 2014). While so much has been done in China and other countries concerning these species, scientific reports on these plants in Africa are scanty. It is the intention of this paper to provide an overview summary of applications of this genus in traditional medicine, phytochemistry and biological activities, and spearheading new research areas concerning African *Isodon* species.

Methodology

There are various literatures available on the uses of *Isodon* plants in traditional medicine, their phytochemistry, pharmacological activities, and various synthetic approaches designed for bioactive *Isodon* compounds (Dilshad et al. 2008, Chen et al. 2009, Kang et al. 2010, Gu et al. 2010, Akhtar et al. 2013, Ahmad et al. 2014, Shuaib and Khan 2015, Zhao et al. 2017, Abbasi et al. 2019, Janbaz et al. 2014). Although there are not many reviews on the subject, an excellent review by Liu et al. (2017) dealt extensively with chemical constituents, biological activities and synthesis of *Isodon* bioactive compounds from 2005 to 2016. Other reviews including those of Smith and Njardarson (2018), and Li et al. (2018), focused on synthetic strategies towards maoecrystal V (**1**) and spirolactone-type diterpenoids, respectively. Despite these excellent reviews, it is the intention of this paper to provide updated detailed information on the phytochemistry and biological activities of compounds from the genus *Isodon* from 2016 to 2019, and recent synthetic approaches of pharmacologically active *Isodon* diterpenoids and derivatives.

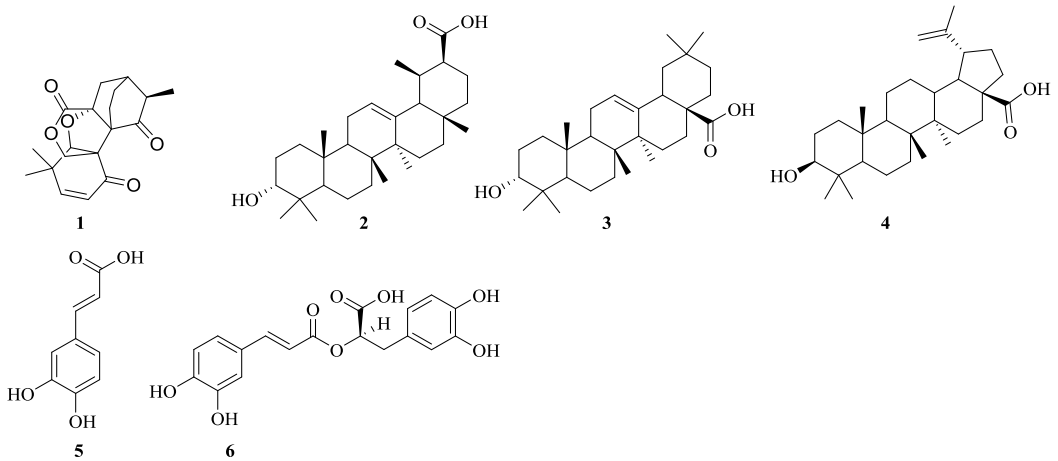
For the stated objective to be achieved, collection, documentation and analysis of information concerning the uses of these plants in traditional medicine, phytochemistry, biological activities, and synthetic approaches of these compounds were done. Thus, literature searches were done by using search engines such as Science Direct, Springer Link, and Google Scholar, whereby combinations of key words like *Isodon* diterpenoids, *Isodon* medicinal uses, *Isodon* phytochemistry, *Isodon* diterpenoids synthetic approaches were used to obtain information needed. A total of over 1000 publications were obtained on the subject; however, upon screening basing on their publication dates and relevance to the review topic, about 100 were selected. Before the literatures were deemed as unfit for the topic, they were thoroughly read and analysed.

Results and Discussion

Review on the use of *Isodon* plants in traditional medicine

The contributions of plants in the battle against diseases in man, livestock and wildlife can be traced back since the existence of man. Thus, use of medicinal plants in various communities for disease control is as old as the human civilization itself. In Chinese traditional medicine system, fresh leaves of *I. rugosus* Wall. ex Benth. are renowned for relieving tooth pains, and the bark of the plant is used against dysentery and to alleviate body, abdominal and gastric pains (Akhtar et al. 2013, Ahmad et al. 2014, Shuaib and Khan 2015). The plant is used against various skin, ear, nose, throat and intestine infections (Kang et al. 2010). One to two (1-2) drops of the fresh leaves extract of the plant are used against ear pains, also rubbing the extract on the affected area is known to relieve pains. The plant is also used against microbial infections, blood pressure, dysentery, hypoglycemic, pyrexia, and rheumatism (Khan and Khatoon 2007, Adnan et al. 2012,

Shuaib et al. 2014). Furthermore, the plant is used as anti-septic and bronchodilator agent (Xu et al. 2010, Liu et al. 2012). For curing reproductive disorders in cattle, the boiled decoction of the plant is used (Dilshad et al. 2008). Pharmacological activities evaluations on the plant extract showed anti-emetic, anti-spasmodic, anti-pyretic (Janbaz et al. 2014) and anti-fungal (Rauf et al. 2012) potentials. Moreover, the plant extracts have been shown to exhibit anti-bacterial, anti-oxidant and lipoxygenase inhibitor activities (Gu et al. 2010). The analgesic potential evaluation of the chloroform fraction showed 53% analgesia in acetic acid induced writhing, and in formalin test the extract inhibited pain by 61% and 45% at phase-I and –II, respectively (Kong et al. 2014). Moreover, Siddiquah et al. (2018) investigated zinc oxide nanoparticles made from *I. rugosus*. It was reported that the particles showed superior anti-cancer and anti-microbial activities as compared to the extract alone. This led to the conclusion that biogenic zinc oxide natural products have extraordinary potential against cancer and microbes (Siddiquah et al. 2018). Essential oils extracted from *I. rugosus* demonstrated strong anti-nociceptive activity, by acting on the central pathway of nociception. Moreover, the oils showed free radicals scavenging activity with IC_{50} values of 338 and 118 µg/mL for 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) free radicals, respectively. Cholinesterases inhibitory activities of these essential oils were reported to give IC_{50} values of 93.56 and 284.19 µg/mL by AChE and BChE, respectively (Sadiq et al. 2018). Last, but not the least, the production of anti-oxidant and anti-aging compounds (cosmetic potential) of *I. rugosus* (Wall. ex Benth.) Codd was evaluated using *in vitro* callus induction from stem and leaf explants under various plant growth regulators. The stem derived explants, the plant growth regulator thidiazuron alone or in combination with naphthalene acetic acid induced highest callogenesis. Thus, the anti-oxidant activities of these samples under optimum hormonal combinations were reported to be 3.0 mg/L TDZ + 1.0 mg/L NAA. Their constituents were found to be plectranthoic acid (**2**) at 373.92 µg/g dry weight (dw), oleanolic acid (**3**) at 287.58 µg/g dw, betulinic acid (**4**) at 90.51 µg/g dw, caffeic acid (**5**) at 91.71 µg/g dw, and rosmarinic acid (**6**) at 1732.61 µg/g dw. It was further reported that compound **6** was the main contributor in the observed anti-oxidant and anti-aging activities (Abbasi et al. 2019).



I. flavidus (Hand.-Mazz.) H. Hara, a perennial herb from Yunnan and Guizhou province (China) has been used as an anti-fungal agent (Li et al. 2016a). *I. coetsa* is used

in traditional Chinese medicine system against inflammation, tumours and bacterial infections (Neelamkavil and Thoppil 2014). *I. kameba* and *I. pervifolius* are locally used in China against tumours; this correlated well with the scientific findings, where the plants extracts were found to exhibit anti-tumour, cytotoxic and anti-bacterial activities (Zhou et al. 2014).

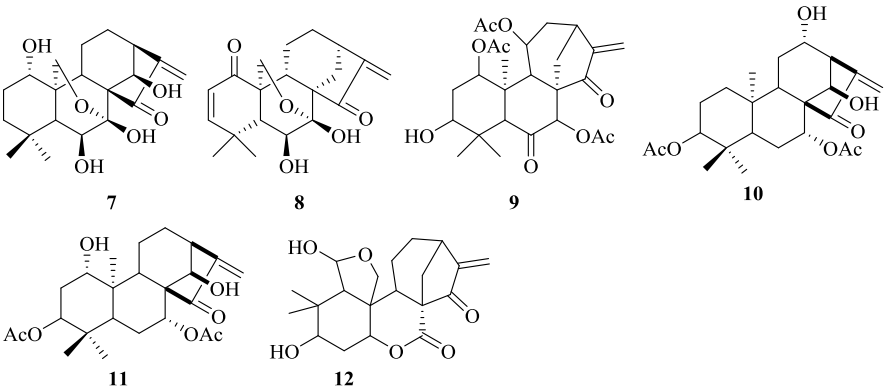
In Chinese traditional medicine system, the leaves of *I. rubescens* (Hemsl.) H. Hara or "donglingcao" in Chinese have been used for the healing of respiratory and gastrointestinal bacterial infections, inflammation, and cancer. Due to its wide use in Chinese ethnomedicine systems, the plant extract was developed into a drug formulation for treatments of sore throats and inflammation (Chen et al. 2009, Tan et al. 2011). Scientific studies revealed that the anti-cancer activities of the plant extract proceed through inhibiting NF-κB signalling. The isolation of oridonin (**7**), a compound renowned for anti-cancer activity confirmed the ethnomedical uses of the plant (Sun et al. 2006).

From the above discussion, it is evident that plants of the genus *Isodon* from Africa do not feature in the literature so far surveyed. Now, considering the facts that the genus is a valuable resource for pharmacological research, and scientific reports on these plants in Africa are scanty, then, it is important for phytochemists and pharmacologists to focus on these plants, so as to reveal the structures of their compounds and their respective pharmacological significance.

Review on phytochemistry of the genus *Isodon* from 2016-2019 and synthesis

The isolation of compound **1** and derivatives (Zhou et al. 2007, Kang et al. 2010, Xu et al. 2017), eriocalyxin B (**8**) (Kong et al. 2014), adenanthin (**9**) (Liu et al. 2012), and pharicins A (**10**) (Xu et al. 2010) and B (**11**) (Gu et al. 2010), coupled with medicinal applications of the plants of genus *Isodon*, have fuelled extensive phytochemical as well as pharmacological studies towards these plants.

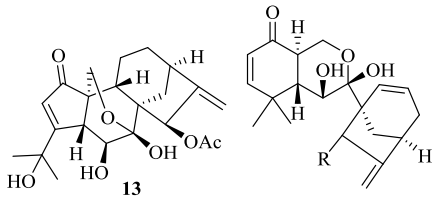
The investigations on *Isodon* diterpenoids began as early as 1910 when bitter principle from "enmei-so" was isolated by Yagi and named it plectranthin (Yagi 1910). However, the structure of plectranthin (also called enmein) was not yet established until 1966 when for the first time X-ray crystallography showed the structure to be 6,7-*seco*-*ent*-kauranoid (**12**) (Natsume and Iitaka 1966).



An excellent review of the phytochemistry of this genus from 2005 to 2016 was provided by Liu et al. (2017), however, vast diversity of *Isodon* diterpenoids have been discovered since 2016 to date. Therefore, about 120 new compounds with

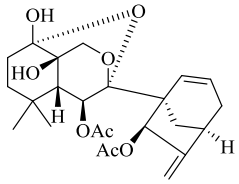
different oxygenation and their respective biological activities are described herein.

Aerial parts of *I. eriocalyx* yielded maoeriocalysins A–D (**7–16**), however, to date, there are no reports on the pharmacological properties of the compounds (Yang et al. 2019). From the same plant, Li et al. (2018) investigated anti-inflammatory activities of the plant extract and its bioactive constituent eriocalyxin B (**17**). Both plant extract and compound **17** enhanced the cytotoxic and apoptotic effects of gemcitabine in pancreatic cancer cells by regulating PDK1/AKT1/caspase and JNK signaling (Li et al. 2018).



13

	R
14.	=O
15.	OAc



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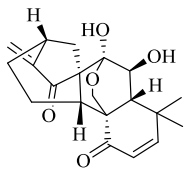
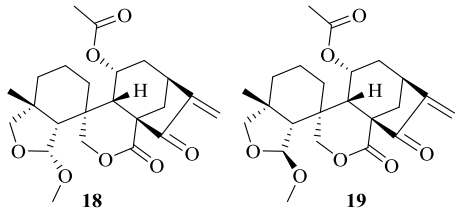


17

Two 6,7-*seco*-spiro-lacton-*ent*-kauranoids namely, 6-*epi*-11-O-acetylangustifolin (**18**) and 11-O-acetylangustifolin (**19**), and a glycosidic iridoid, 6-O-veratroylbarlerin (**20**), and 7,20-epoxy-*ent*-kaurane diterpenoids, isojiangrubesins A-G (**21–27**) were isolated from aerial parts of *I. rubescens* (Hemsl.) H. Hara. Compounds **18** and **19** exhibited cytotoxic activities against human lung cancer cell lines A549 and leukemia cell lines K562 (Luo et al. 2018). However, there are no reports on the biological activities potential for compound **20** (Belaabed et al. 2018). Compounds **21**–**27** were evaluated for their inhibitory effects on LPS-activated NO production in RAW264.7 cells. Therefore, compounds **22** and **25**, exhibited potent activities with IC_{50} values of 1.2 and 1.3 µg/mL, respectively. Better still, the compounds showed lower toxicity upon *in vitro* testing against five human tumour cell lines (HL-60, SMMC-7721, A-549, MCF-7, and SW480) (Zhang et al. 2017).



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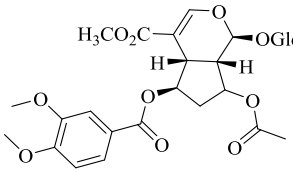

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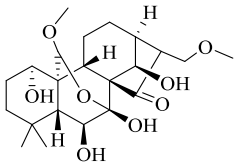

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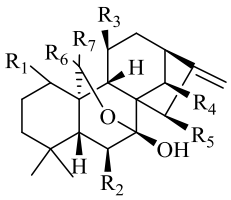
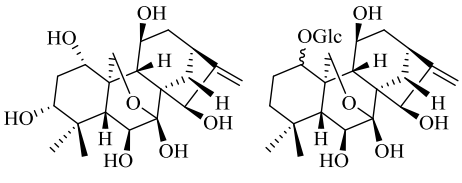


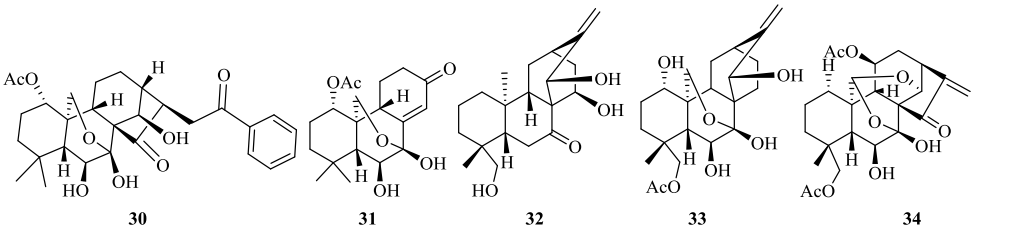
	R_1	R_2	R_3	R_4	R_5	R_6	R_7
22.	α-OH	OH	H	H	=O	OMe	H
23.	α-OH	OH	H	H	=O	H	OMe
24.	β-OH	OH	H	OH	OH	H	H
25.	α-OH	OH	H	OH	=O	OBu	H
26.	α-OH	OH	H	OH	OH	OBu	H
27.	α-OH	OH	H	OH	OH	H	OBu

Matsumoto and group (2017) reported terpenes I (**28**) and II (**29**) from aerial parts of *I. japonica*. The compounds exhibited anti-mutagenic activities (Matsumoto et al. 2017).

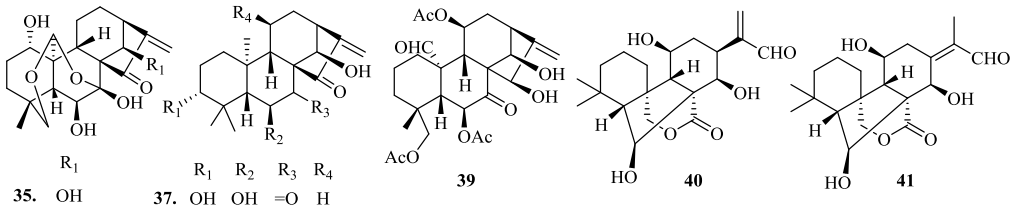


28 **29**

Aerial parts of *I. pharicus* yielded compounds **30**–**41**, and twenty one 7α,20-epoxy-*ent*-kaurane diterpenoids, pharicins C−W (**42**−**62**). Compounds **37** and **38** exhibited significant inhibitory effects against HL-60, SMMC-7721, A-549, MCF-7, and SW-480 human tumour cell lines, at IC_{50} values ranging from 0.37 to 6.03 μM (Hu et al. 2018a). Compounds **52** and **57** showed inhibitory activities at IC_{50} values ranging from 1.01 to 9.62 μM against HL-60, SMMC-7721, A-549, MCF-7, and SW-480 tumour cell lines, the rest exhibited moderate cytotoxic potency (Hu et al. 2018b).



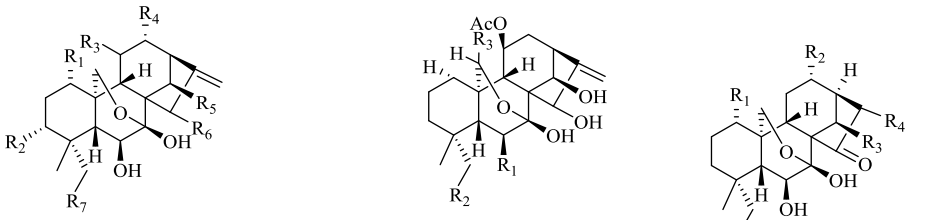
30 **31** **32** **33** **34**



35. R_1 = OH
36. R_1 = H

	R_1	R_2	R_3	R_4
37.	OH	OH	=O	H
38.	H	H	H	OH

39 **40** **41**



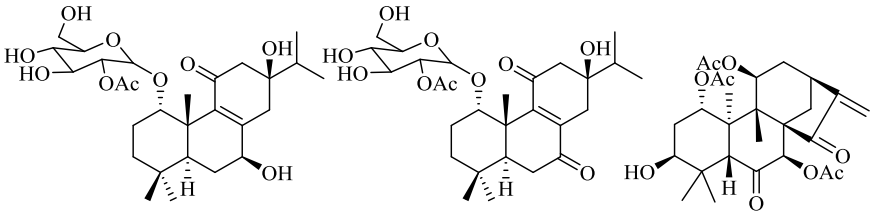
	R_1	R_2	R_3	R_4	R_5	R_6	R_7
42.	H	H	H	OH	H	β-OH	OAc
43.	H	OH	H	H	H	=O	OAc
44.	OH	H	H	H	OH	=O	OAc
45.	H	OH	H	H	OH	=O	OAc
46.	OH	H	H	H	OH	=O	OH
47.	H	OH	H	H	OH	=O	OH
48.	H	H	H	OH	OH	=O	OH
49.	OH	H	H	H	OH	β-OH	OAc
50.	H	OAc	H	H	OH	=O	OH
51.	OAc	H	β-OH	H	H	β-OH	H

	R_1	R_2	R_3
52.	OAc	OAc	OH
53.	OH	OAc	OH
54.	OH	H	OEt
55.	OH	H	OH

	R_1	R_2	R_3	R_4	R_5
56.	OH	H	H	β-CH_2OCH_3	OAc
57.	OAc	H	H	β-CH_2OCH_3	H
58.	OAc	H	H	α-CH_2OCH_3	H
59.	H	OH	OH	α-CH_2OCH_3	OH
60.	OH	H	OH	α-CH_2OCH_3	OH
61.	OH	H	OH	β-CH_2OCH_3	OH
62.	H	OH	OH	α-CH_2OCH_3	OAc

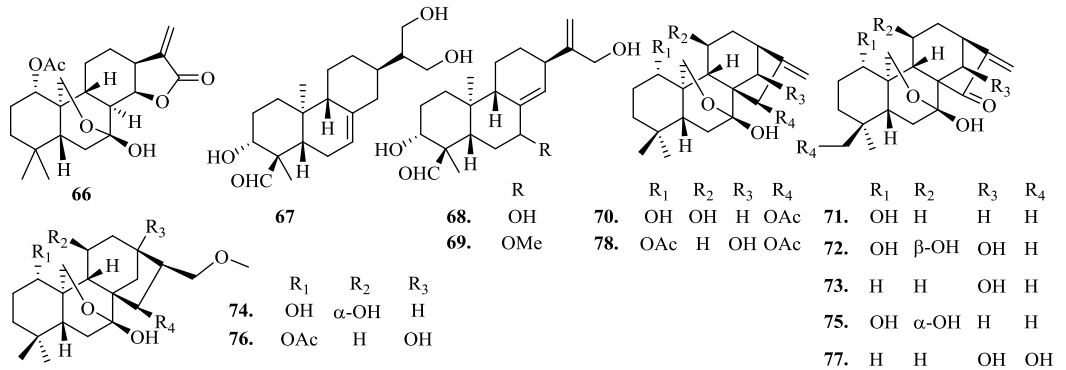
Talienosides A (**63**) and B (**64**) were isolated from underground parts of *I. taliensis*. Compound **63** inhibited α-glycosidase and β-hematin formation with **64**

demonstrating weaker inhibitory activity (Xiang et al. 2018). Hu et al. 2019 isolated adenanthin (**65**) from aerial parts of *I. adenantha*, the compound showed increase in intracellular reactive oxygen species in leukemic and hepatocellular carcinoma cells. Furthermore, the compound inhibited adipogenesis of 3T3-L1 and mouse embryonic fibroblasts', therefore, reducing significantly weight and adipose tissue mass in mice (Hu et al. 2019).



63 **64** **65**

Aerial parts of *I. serra* yielded four *ent*-abietanoids, namely, serrin K (**66**), xerophilusin XVII (**67**), and enanderianins Q and R (**68** and **69**), and nine 7,20-epoxy-*ent*-kaurane diterpenoids, namely, 15-acetylmegathyrin B (**70**), serrin E (**71**), 14b-hydroxyrabdocoestin A (**72**), serrin F (**73**), serrin G (**74**), 11-epi-rabdocoestin A (**75**), serrin H (**76**), serrin I (**77**), and 15-acetylenanderianin N (**78**). Compound **66** inhibited NO production in LPS-stimulated RAW264.7 cells (IC_{50} = 1.8 µM), with weak cytotoxicity on five human tumour cell lines (HL-60, SMMC-7721, A-549, MCF-7, SW480) (Wan et al. 2017). Compounds **73**, **74**, **76** and **77** strongly inhibited NO production in LPS-stimulated RAW264.7 cells, however, with exception of **73** that exhibited cytotoxicity against HL-60, SMMC-7721, A-549, MCF-7, SW480, the rest showed no cytotoxicity (Wan et al. 2016).



66 **67**

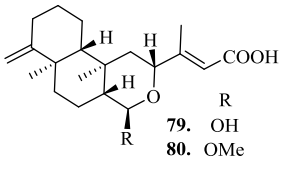
	R
68.	OH
69.	OMe

	R_1	R_2	R_3	R_4
70.	OH	OH	H	OAc
78.	OAc	H	OH	OAc

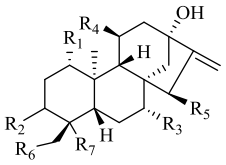
	R_1	R_2	R_3	R_4
71.	OH	H	H	H
72.	OH	β-OH	OH	H
73.	H	H	OH	H
75.	OH	α-OH	H	H
77.	H	H	OH	OH

	R_1	R_2	R_3
74.	OH	α-OH	H
76.	OAc	H	OH

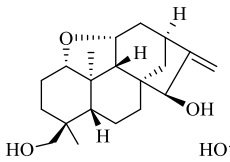
Isoscoparins R (**79**) and S (**80**), and diterpenoids **81**−**94**, and scopariusols L–T (**95**–**103**) were isolated from aerial parts of *I. scoparius*. Compound **80** showed weak activity as autophagic inhibitor (Li et al. 2019). Compounds **81**, **82** **84** and **95** exhibited cytotoxic activity against five human tumor cell lines (HL-60, SMMC-7721, A-549, MCF-7, and SW-480). The four compounds inhibited NO production in LPS-stimulated RAW264.7 cells, at IC_{50} = 1.0, 3.1, 1.8 and 0.6 µM, respectively (Jiang et al. 2017, Jiang et al. 2018).



79. OH
80. OMe



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
81.	H	β-OH	H	OAc	=O	H	CH_3
84.	OH	H	OH	OAc	=O	H	CH_3
85.	H	β-OH	H	OAc	OH	H	CH_3
86.	H	α-OH	H	OAc	OH	H	CH_3
87.	H	α-OH	H	OH	OH	H	CH_3
88.	H	H	H	OH	OH	OH	CH_3
89.	H	H	H	OAc	OH	OH	CH_3
90.	H	H	H	OAc	OH	H	CHO
91.	H	H	H	OAc	OH	H	CH_2OAc



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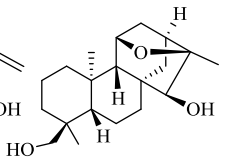

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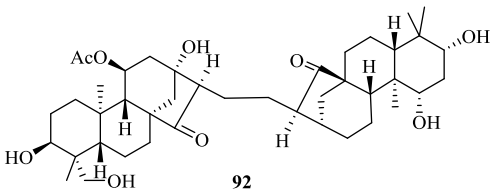

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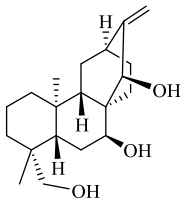

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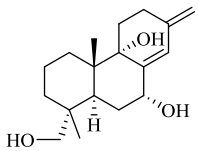

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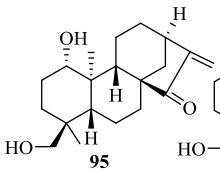

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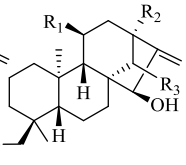
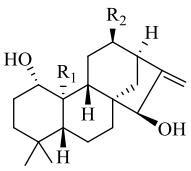
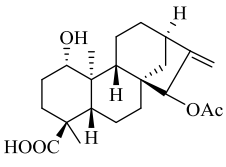


	R_1	R_2	R_3
96.	=O	OH	H
97.	=O	H	H
98.	OH	H	H
99.	H	H	OH



	R_1	R_2
100.	H	CHO
101.	OH	CH_2OH



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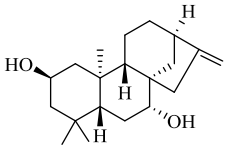
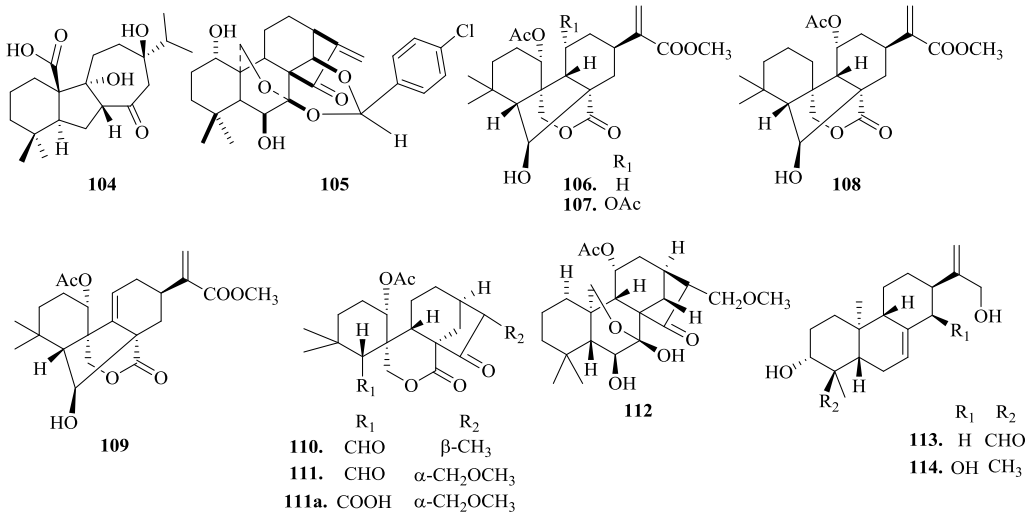


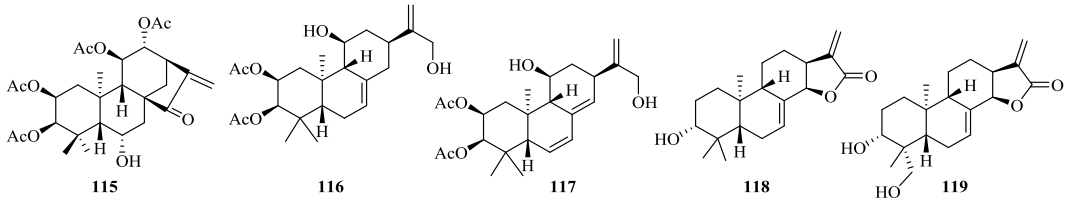
103

Amethinol (**104**) was isolated from *I. amethystoides*, the compound showed 78% inhibition of luciferase activity at 10 µg/ml (Zhao et al. 2018). The structural modification of compound **1** gave jesridonin (**105**), which effectively prevented the growth of paclitaxel-resistant human oesophageal carcinoma cells EC109 with low toxicity. Also the compound significantly inhibited the proliferation, induced apoptosis and arrested the cell cycle at the G2/M phase on EC109 cells. The mechanism for the expressed activity included up-regulating the expression of p53, modulator of apoptosis (PUMA), cleaved-caspase-9 and caspase -3. Furthermore, the compound down-regulated the expressions of procaspase-3, -9 and Bcl-2 in the EC109 in concentration-dependent manners (Wang et al. 2017).

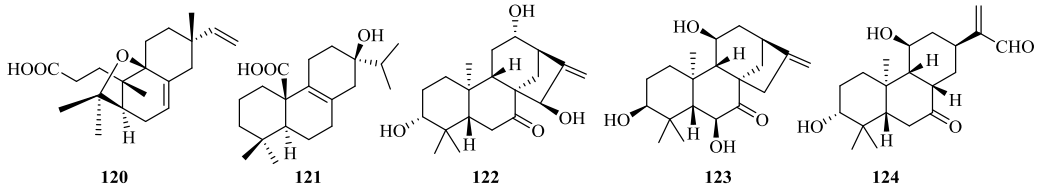
I. ternifolius (aerial parts) yielded ternifoliusins A-I (**106–114**), with compounds **106–109** possessing a rare 6, 7, 8, 15- *diseco*-7,20-olide-6,8-cyclo-*ent*-kaurane skeleton. Lower cytotoxicity activity against the HL-60, SMMC-7721, A-549, MCF-7, and SW-480 human tumour cell lines was observed for all the compounds (Gou et al. 2019).

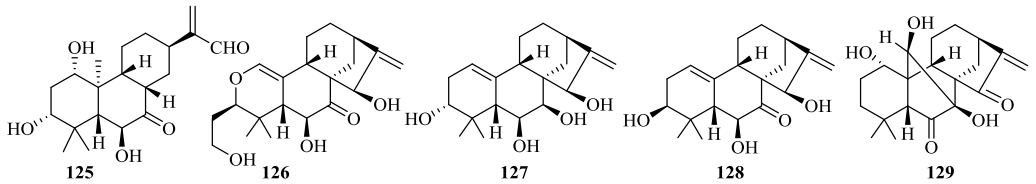


Isoforretin A (**115**) and four *ent*-abietane diterpenoids named as isoforrethins A–D (**116** - **119**) were isolated from aerial parts of *I. forestii* var. forestii. Compound **115** exhibited anti-tumour effects by triggering ROS mediated anti-tumor effects and inhibiting thioredoxin-1 (Sun et al. 2017). Significant inhibitory activities against SMMC-7721, A-549, MCF-7, and SW-480 was shown by compound **119** (Chen et al. 2019).



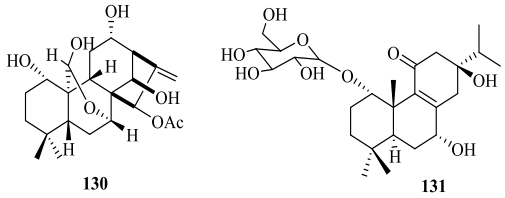
Fladin A (**120**), consisting of an unprecedented cyclic ether group between C-4 and C-9, and lophanic acid (**121**) were isolated from aerial parts of *I. flavidus*. Compound **121** exhibited MIC value of 7.8 µg/mL, against athlete's foot fungus *Trichophyton rubrum* (Li et al. 2016a).
Four phyllostachysins I - L (**122–125**) and phyllostachysins M–P (**126**–**129**) were isolated from aerial parts of *I. phyllostachys*. Compounds **124** and **125** showed significant cytotoxic activities, and strongly inhibited the production of NO in LPS-stimulated RAW264.7 cells (Yang et al. 2016). Compounds **126**–**129** exhibited lower cytotoxic activities with IC_{50} > 10 µM (Yang et al. 2017).





125 **126** **127** **128** **129**

A 7,20-epoxy kaurane diterpenoid, 15-acetyldemethylkamebacetal A (**130**) was extracted from aerial parts of *I. inflexus*. The compound showed NF-κB inhibitory activities with IC_{50} = 20.15 μM (Xu et al. 2016). An abietane glycoside, rugosodon (**131**), and compound **6** were isolated from the roots and aerial parts of *I. rugosus* Wall Ex Benth, respectively. Compound **131** exhibited significant α-glucosidase inhibitory activity with IC_{50} value of 0.453 mg/mL (Ullah et al. 2019). Compound **6** showed activity against pea aphid, *Acyrthosiphon pisum*, with LC_{90} value of 5.4 ppm (Khan et al. 2019).

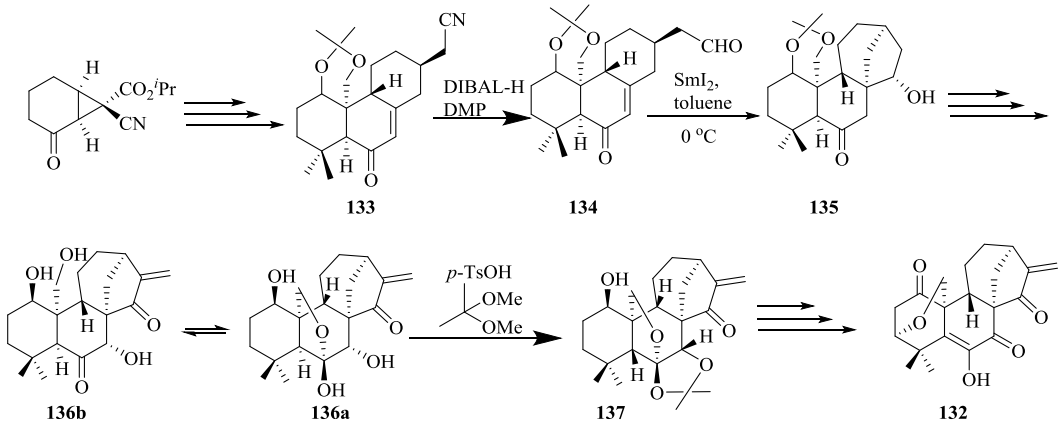


130 **131**

In summary, diterpenoids from the genus *Isodon* have shown impressive anti-inflammatory, anti-fungal, insecticidal and other pharmacological effects with minimum cytotoxicity. However, the above discussion reveals that plants of the genus *Isodon* from Africa have so far not been scientifically investigated. Therefore, this serves to draw the attention of phytochemists and pharmacologists to work together to reveal the structures of the compounds and the detailed mechanisms of their biological activities for the benefits of drug discovery processes. It is interesting to note that, in some literatures discussed above, reinvestigations of the same species yielded different compounds (Zhang et al. 2017, Yang et al. 2019, Li et al. 2018, Luo et al. 2018, Belaabed et al. 2018, Hu et al. 2018a, Hu et al. 2018b). In chemotaxonomic point of view, it should be noted that changes in ecological environment can bring changes in secondary metabolites produced by the plant. Therefore, it is expected that African *Isodon* species would yield different compounds with different oxygenation. This is an open area of research to unveil the structures and pharmacological potentials of components from *Isodon* species occurring in Africa. Furthermore, owing to the interesting pharmacological, molecular structures expressed by these compounds, and sustainable use of the resources, synthesis of these compounds becomes vital.

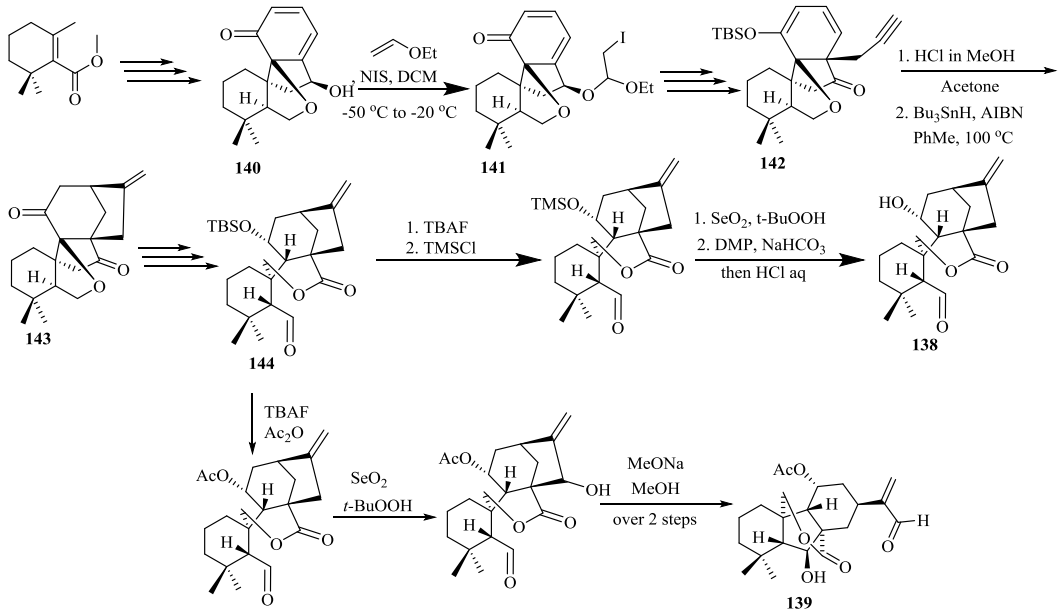
An in-depth review on synthetic methods of compound **1** and spirolactone-type diterpenoids have been provided by Smith and Njardarson (2018), and Li et al. (2018), respectively. However, in this review, a summary of the synthesis of the compounds that were not reviewed in the mentioned papers is given. For complete synthetic schemes of the summarized syntheses, the original articles must be consulted. Su et al. (2018) utilized highly diastereo- and regioselective intermolecular Diels–Alder cycloaddition reactions in synthesizing the anti-tumour natural product maoecrystal P (**132**). The reactions involved a diene present in a substituted bicyclo[4.1.0] system in assembling most of the carbon centres. The construction of the D-ring was achieved by reduction of **133** under DIBAL-H, followed by oxidation, to yield **134**. Transformation of compound **134** to **135** that consisted of a sterically hindered quartenary carbon and a strained ring system completed the *ent*-kauranoid skeleton system. Isomerization of **136a** under 2,2-dimethoxypropane in the presence of catalytic tosylic acid afforded

137. Intramolecular conjugate addition and oxidation of C7 alcohol ultimately yielded **132** as summarized in **Scheme 1**.



Scheme 1: Summarized synthesis of compound **132.**

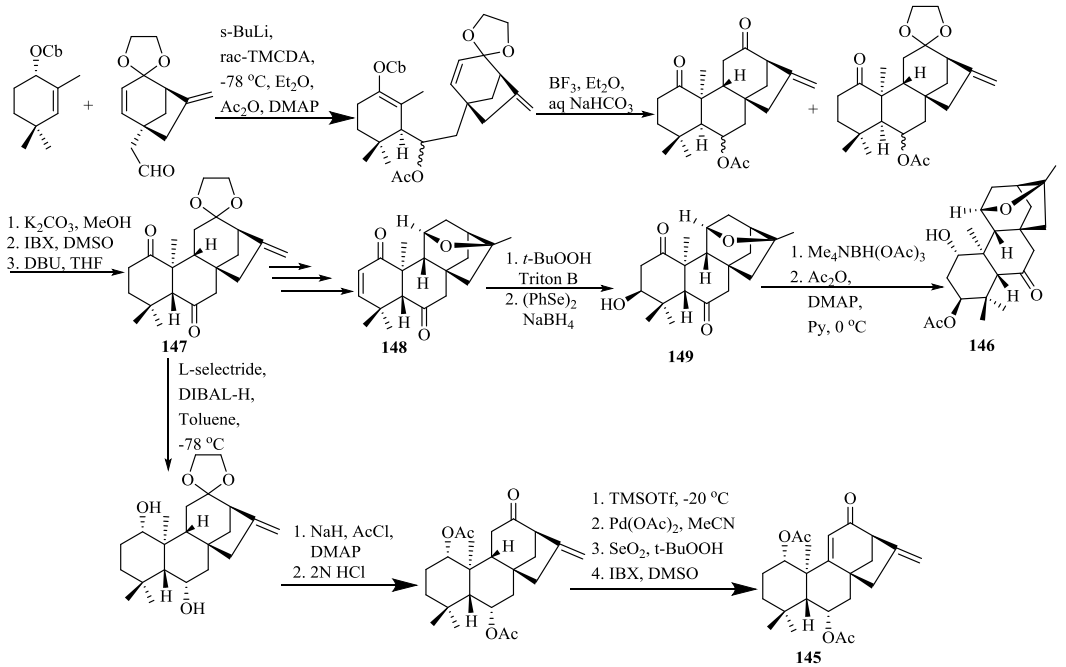
Convenient methods for synthesizing both trichorabdal A (**138**) and maoecrystal Z (**139**) was reported by Lv et al. (2018). The group generated a common intermediate between the two structures, which is bicyclo[3.2.1]octane by a series of retroaldol/aldol reaction. Not only that, but also, they utilized cross-ring radical cyclization to construct all quaternary carbon centres in the *Isodon* diterpenoids, and Ueno–Stork cyclization on to 1,6-enone system, to yield the target molecules. Towards synthesizing a common intermediate, the group proceeded with oxidative dearomatization to yield **140**, and then converted to Ueno-Stork cyclization substrate **141**. 1,4-addition to break 1,6-enone system, followed by radical cyclization, and a series of reduction followed by double Swern oxidation and treatment with Seyfertg-Gilbert reagent to alkyne **142**. Acid hydrolysis afforded enone system, followed by construction of the bicycle[3.2.1]octane ring system using radical cyclization to **143**. In several steps, a common intermediate, **144** was obtained. With the availability of **144**, syntheses of compounds **138** and **139** were completed as described in **Scheme 2**.



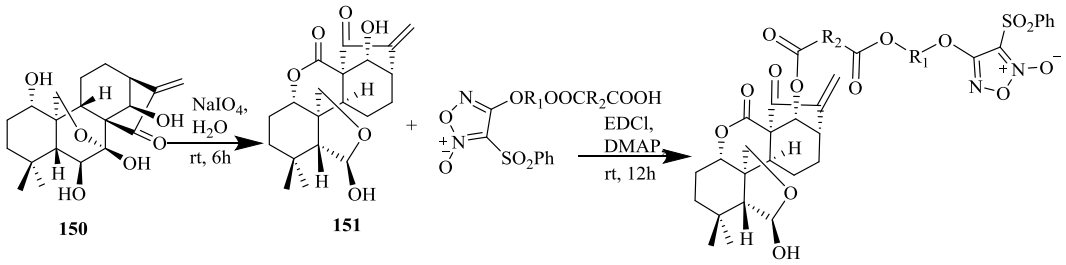
Scheme 2: Summarized synthesis of compounds **138** and **139**.

Zhao et al. (2017) synthesized 1α,6α-diacetoxy-ent-kaura-9(11),16-dien-12,15-dione (**145**) and lungshengenin D (**146**) by installing the [3.2.1] bicyclic motif at earlier stages. The group utilized Hoppe's homoaldol reaction of an aldehyde and cyclohexenyl carbamate, followed by intramolecular Mukaiyama-Michael reaction to obtain the tetracyclic core structure of *ent*-kaurane diterpenoids. The synthesis of the two compounds was achieved through synthesis of the common intermediate **147**. Compound **147** was subjected into various reactions through several steps to obtain **146**. Selective reduction of C-12 carbonyl group of **147**, after a series of reactions, enone **148** was obtained. Lastly, selective epoxidation of **148**, followed by reduction to alcohol **149**, hydroxyl directed reduction to control stereochemistry at C1, followed by regioselective acetylation yielded **146** (**Scheme 3**).

Bioactive enmein-type NO-releasing diterpenoids derivatives were synthesized according to **Scheme 4**, and their biological potentials were reported by Li et al. (2016b). Of all the derivatives prepared, it was indicated that compounds **153** and **155** were the most anti-bacterial with MIC values of 2 and 4 µg/mL, respectively against *S. aureus* and *B. subtilis*. The observed activity might be due to the influence of the total length of the compound (Li et al. 2016b). All compounds showed higher effectiveness against K562 leukemia cell line, MGC-803 gastric cancer cell line, CaEs-17 oesophageal cancer cell line, and Bel-7402 hepatoma cell line than compound **7**. Derivative **157** showed stronger activity with IC_{50} of 0.72 µM than that of taxol (1.89 µM), and generally it was reported that derivatives **154**, **157**, and **160** demonstrated superior activities than the rest; this might be due to the presence of aromatic rings that might be influencing the binding properties of the molecules (Li et al. 2016b).



Scheme 3: Summarized synthesis of compounds **145** and **146**.



	R_1	R_2		R_1	R_2
152.	$(CH_2)_2$	$(CH_2)_2$	**157.**	$(CH_2)_3$	o-C_6H_4
153.	$(CH_2)_2$	$(CH_2)_3$	**158.**	$(CH_2)_4$	$(CH_2)_2$
154.	$(CH_2)_2$	o-C_6H_4	**159.**	$(CH_2)_4$	$(CH_2)_3$
155.	$(CH_2)_3$	$(CH_2)_2$	**160.**	$(CH_2)_4$	o-C_6H_4
156.	$(CH_2)_3$	$(CH_2)_3$			

Scheme 4: Total synthesis of enmein-type NO-releasing diterpenoids.

Discussion

The literatures summarized in this paper have shown the diterpenoids richness of the genus *Isodon* and their respective pharmacological properties. It is also shown that plants of genus *Isodon* have great potential in health care and disease control. Nevertheless, the applications of these plants for health and disease control in African

countries require further scientific investigation/analysis.

So far, *Isodon ramosissimus* (Hook. f.) candd. (Figure 1) is the only species that has been identified in Tanzania. Its specific locations are in Kungwe Mountain, Kahoko, Ukaguru Mountains, Mandege-Vingwete, Lulanda Escarpment, and Fufu stream. In Africa, the plant is distributed in Sierra Leone, Nigeria, Cameroon, Equatorial Guinea, Congo-Kinshasa, Rwanda, Burundi, Sudan (Imatong Mountains), Ethiopia, Angola, Zambia, Malawi, Zimbabwe, Kenya and Uganda. The habitats in which the plant is mostly found include forest undergrowth and margins, upland grassland, descending to lower altitudes along rivers at about 750 – 2100 M (Paton et al. 2009).

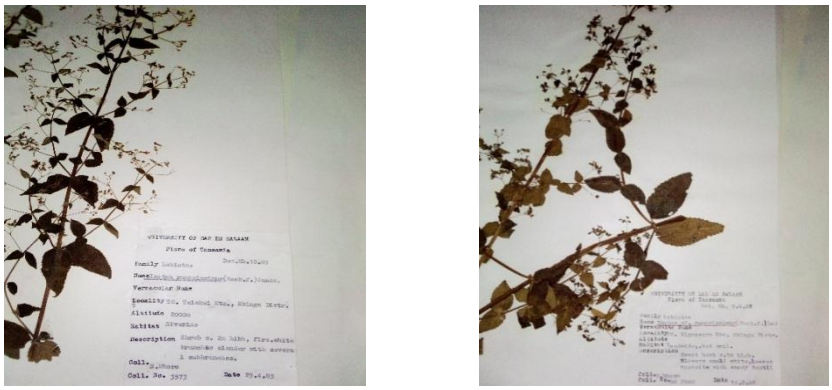


Figure 1: Herbarium specimens of *Isodon ramosissimus* (Hook. f.) candd (Pictures from the Herbarium, Botany Department, University of Dar es Salaam).

Another *Isodon* species identified in Africa is *Isodon schimperi* (shrub, subshrub, and perennial herb), which is distributed in Central Africa, Ethiopia, Rwanda and Burundi. Generally, the plant grows in medium altitude, and montane forest, usually along margin, and montane grasslands (Yu et al. 2014). Since scientific reports on these plants are scanty, phytochemists are enlightened on this area of research. It is known that the same species of plants in different geographical and ecological conditions possess different secondary metabolites, biological potentials and sometimes different mechanisms of action, then, structures, potentials against tropical diseases and mechanisms of activities are waiting to be revealed. As indicated above, *Isodon* species have shown reputed biological potential, and in China, *Isodon* based products have been formulated for disease control. Since large proportions of the population worldwide use herbal medicines/formulations as medicines or supplements, phytochemists and pharmacologists are enlightened to this open area of research towards developing products for various uses including health, beauty and others. For example, although it needs further investigations, products of compound **65** that has been proven to reduce significantly weight and adipose tissue mass in mice, could be developed to reduce health effects related to obesity. The products might be in the form of concoctions, teas, powder, tablets and others. To reduce the problem of bioavailability and enhance bioactivity of the products, the introduction of pharmaceutical additives proven to enhance bioavailability of natural products is highly recommended. These include quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside.

Conclusion

The genus *Isodon* has provided many efficacious herbal drugs, and different lead

compounds with varieties of biological activities. There are many reports on chemical and biological aspects of *Isodon* species, but African species have not been scientifically investigated. The literature indicates the genus to be rich in diterpenoids with potential therapeutic activities, waiting to be explored. It is incumbent on scientific researchers to fill the gap created by the absence of knowledge concerning African *Isodon* species. This is because geographical as well as seasonal variations contribute largely to chemical compositions differences, thus, a need for authentication of chemical constituents, pharmacological potentials and synthetic methods of the compounds. For these to be fulfilled, the extensions of interdisciplinary researches leading to revealing structures, biological potentials as well as convenient synthetic methods are recommended. It is my hope that this review provides useful information to researchers in various fields, especially those dealing with drug discovery.

Acknowledgement

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