DOI: 10.15255/KUI.2018.027
KUI-2/2019
Review
Received April 28, 2018
Accepted July 20, 2018

Medicinal and Pesticidal Potentials of the Constituents of the Essential Oil from *Adenia cissampeloides* Leaves

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Abstract

Adenia cissampeloides (Planch. ex Hook.) Harms is used in alternative medicine primarily for the management of hypertension and several other diseases. Isolation and GC-MS analysis of five essential oils collected fractionally and over 4 h by hydrodistillation from the dried leaves were carried out. The constituents included phytol, α-linolenic acid, *n*-hexadecanoic acid, hexahydrofarnesyl acetone, (13*S*)-8,13-epoxy-labd-14-ene, kaur-16-ene, guaiol, α-gurjunene, and α-elemene. Several bioactivities of the constituents as well as their potential applications in medicine and the pharmaceutical and pesticidal industries are discussed. Essential oils from some other plants have several constituents in common with those isolated from *A. cissampeloides*. The bioactivities of such plants are used to suggest other possible applications of *A. cissampeloides*.

Keywords

Adenia cissampeloides, GC-MS, medicinal plants, essential oil, bioactivity

1. Introduction

The uses of plants as medication for various health conditions are found in several countries of the world, including Nigeria.[1] In the practice of alternative medicine, medicinal plants have been used for the management of numerous health conditions, and useful bioactive agents have been found present in various plant extracts, including essential oils. For example, *Sesamum radiatum*, a plant used to improve fertility in male subjects, contains a yohimbine derivative which has been suggested as the relevant bioactive agent.[2] *Cissus populnea* is also used for the same purpose, and extracts from the stem have been found to promote appreciable proliferation of Sertoli cells from rats.[3] The essential oils from *Euphorbia hirta* and *Calotropis procera*, plants used in the management of asthma, have been found to be rich in phytol, an anti-inflammatory compound.[4–6]

Adenia cissampeloides (Planch. ex Hook.) Harms, commonly known as monkey rope or snake climber or Adenia, belongs to the *Passifloraceae* family. It grows in tropical and subtropical regions. The acclaimed use of the plant in Nigeria is in the management of hypertension. It has also been found useful in the treatment of nervous disorders, leprosy, stress, cough, gonorrhoea, as well as antimicrobial treatment for wounds and sores.[7] The roots, leaves, and stem-bark are usually employed as curative agents. The sap is also used as a facial cosmetic. A catalogue of various uses of the plant worldwide contains additional medicinal applications of the various plant parts, which are sometimes used singly or in combination with other parts of the plant. These include an infusion of the root, stem or leaves in treating various ailments, including headache and back pain. The roots in various preparations are used in the treatment of fever, malaria, scabies, cholera, anaemia and snake bites. They are also used as diuretic, abortifacient and arrow poison. Bees have been found to be passive when exposed to smoke from the burning roots. The roots in combination with the stem are administered to humans in order to expel intestinal worms. This mixture is also used for the management of venereal diseases and sterility. The leaves have been reported useful as an antipyretic and for the management of malaria, liver ailments, fractures, bronchitis, lung ailments, depression, and insanity. The bark has also been found useful in inducing amnesia and treating scabies. The stem has been employed as fish poison.[8] The phytochemical constituents reported present in *A. cissampeloides* include tannins, which have antibacterial and anti-inflammatory activity, saponins, phlobatannins, terpenoids, steroids, alkaloids, carbohydrates, glycosides, which may lower blood pressure, and flavonoids, which may exhibit diuretic and antibacterial activity.[9] Tetraphyllum B, a cyanogen glycoside, has been isolated from the roots of the plant.[10] The aqueous extract of a herbal preparation obtained from *A. cissampeloides* was administered to seven female patients in Ghana, and the systolic blood pressure was significantly lower in subjects on *A. cissampeloides* compared to control subjects not on the medication.[11]

Hypertension is a major health problem in black populations. The symptoms of hypertension include severe headaches, chest pain, breathing problems, irregular heartbeats, and dizziness.[12,13] Persistent hypertension is a risk factor for heart failure, stroke, and myocardial infarction, and is a major cause of chronic kidney failure.[14] A single medication, sometimes combined with another, is often administered to hypertensive patients in order to maintain the blood pressure below 140/90. However, there are incidences of resistant hypertension in which concurrent use of three anti-hypertensive medications of different classes do not keep the blood pressure below this value.[15] This calls for further intensive search for anti-hypertensive medications, possibly of plant origin.

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In this study, the isolation and GC-MS analyses of the essential oils from the leaves of *A. cissampeloides* have been carried out primarily for identifying possible constituents that may reduce blood pressure, and other constituents that may be useful for the management of various health disorders for which *A. cissampeloides* is employed in alternative medicine. The occurrences and bioactivities of several constituents and their current and potential applications in the pharmaceutical industry and medicine are discussed. Other possible applications of *A. cissampeloides* are suggested based on comparison of the constituents of the essential oils of the plant with those from other plants.

2. Experimental

2.1. Plant procurement and processing

Fresh leaves of the *Adenia cissampeloides* (Planch. ex Hook.) Harms were obtained from vendors of medicinal plants in Mushin market in Lagos. The plant was identified by Mr. T. K. Odewo, formerly of the Department of Botany of the Forestry Research Institute of Nigeria, Ibadan, where vouchers were deposited and assigned the number FHI 107683. The leaves were cut into small pieces and dried at room temperature in a dust-free environment in the laboratory, after which pulverization was carried out.

2.2 Isolation of essential oils

The essential oils were obtained by hydrodistillation using Clevenger apparatus. The procedure for isolation of the essential oils has been described in a previous report.[5] Two modes of collection were employed. In one mode, the essential oil was collected hourly into hexane over a period of 4 h. In another mode, the essential oil was collected over a period of 4 h. The colour of the fractions in hexane increased in intensity from light orange for the first hour collection to deep orange for the 4th hour collection.

2.3 GC-MS analysis of the essential oils

Analysis was carried on GC-MS model 7890A, Agilent Technologies, fitted with an HP-5MS column (30 m × 0.25 mm, 0.25 μm); carrier gas was helium at a flow rate of 1 ml min^{-1}, and a temperature program 50 °C (1 min) → 300 °C min^{-1} at 8 ° min^{-1} (5 min) was employed. Mass spectra were obtained on spectrometer model 5975 VLMSD. Identification of the compounds was carried out using the ChemStation software and the NIST 08 library in the instrument. The compound in the library with a minimum spectral match of 90 % compared with that of the constituent eluted from the GC was selected as the corresponding compound.

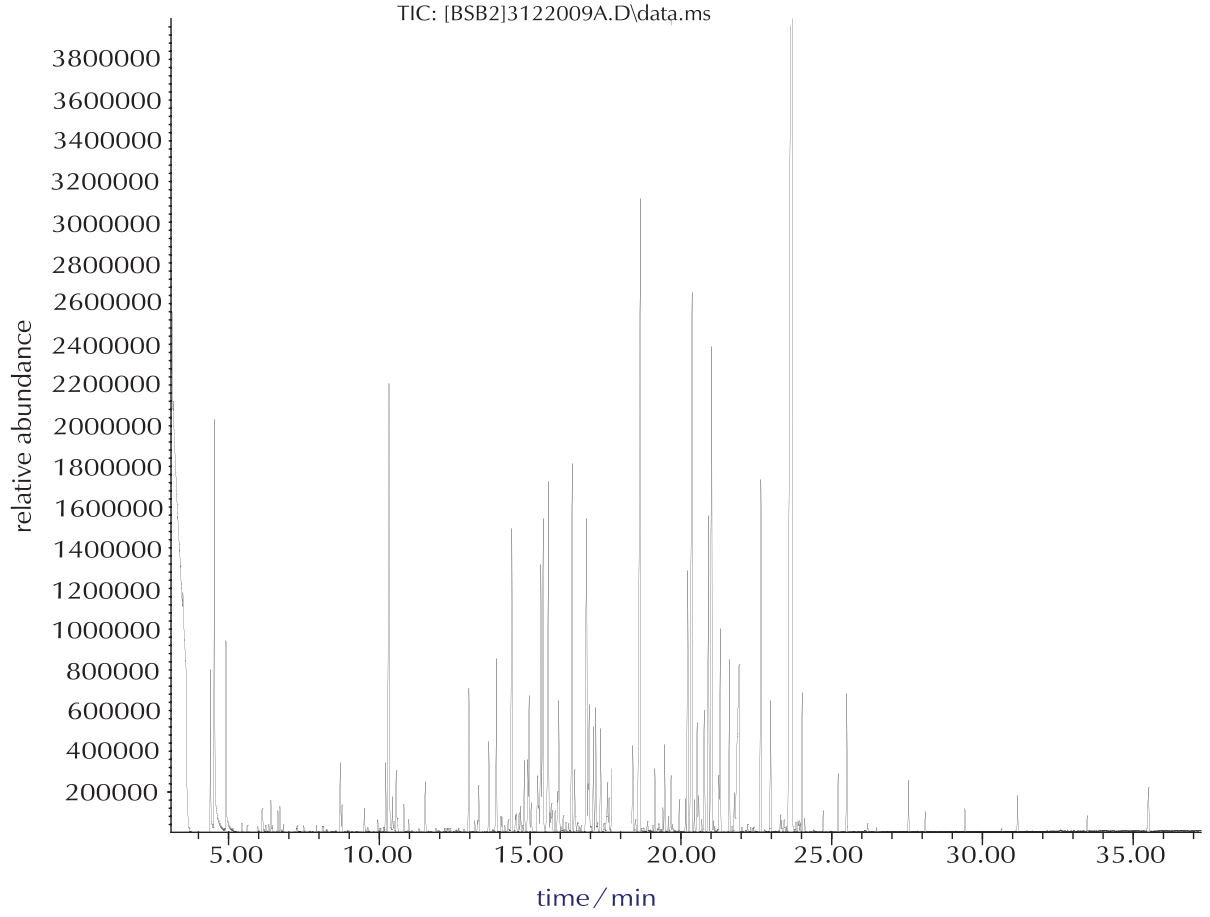

Fig. 1 – Chromatogram of the essential oil from the leaves of *A. cissampeloides* collected in 4 h

3. Results and discussion

The chromatogram for the essential oil collected in 4 h is shown in Fig. 1, while constituents in all five essential oil samples are presented in Table l. The constituents include terpenes, oxygenated terpenes, alcohols, heterocyclic compounds, hydrocarbons, aldehydes, ketones, saturated and unsaturated fatty acids, and fatty acid methyl esters. Several of the constituents of the leaf essential oil of *Adenia cissampeloides* (Planch. ex Hook.) Harms, such as azulene, myrtenol, camphene, cubebene, α-humulene, fatty acids, alcohols, aldehydes, secondary ketones, phytol, and phenolics are typical compounds found in essential oils. The major constituent in the essential oil samples is phytol. Other constituents include α-linolenic acid, *n*-hexadecanoic acid, hexahydrofarnesyl acetone, (13*S*)-8,13-epoxy-labd-14-ene, kaur-16-ene, guaiol, α-gurjunene and α-elemene. The major compound in the essential oil isolated in the 1st hour was germacrene D and 1,13-tridecanediol, diacetate in the 2nd hour. (13*S*)-8,13-epoxy-labd-14-ene and phytol were the major compounds in the 3rd hour , *n*-hexadecanoic acid and phytol in the 4th hour, and phytol in the sample collected over 4 h. The medicinal and pharmaceutical applications of several of these constituents are here discussed. Essential oils from some plants were observed to have several constituents in common with those isolated from *A. cissampeloides*. The bioactivities of such plants are used to suggest other possible applications of *A. cissampeloides*.

Table 1 – Constituents of the essential oils from the leaves of *A. cissampeloides*

S/No	R_T/ min	Compound	Percentage of total				
			1st h	2nd h	3rd h	4th h	4 h
1.	6.40	tSabinene	–	–	–	–	0.2
2.	6.70	1-ethyl-3-methylbenzene	–	–	–	–	0.2
3.	8.77	otβ-Linalool	1.1	–	–	–	–
4.	10.21	otTerpinen-4-ol	–	–	–	–	0.4
5.	10.35	Azulene	1.9	1.3	–	–	3.8
6.	10.53	otα-Terpineol	1.0	–	–	–	–
7.	10.64	ot(−)-Myrtenol	2.3	–	–	–	–
8.	12.27	Indole	–	–	–	0.4	–
9.	12.97	tγ-Elemene	–	–	–	–	0.9
10.	13.03	2,5,5-Trimethyl-1,3,6-heptatriene	–	1.5	–	–	–
11.	13.08	tCamphene	3.7	–	–	–	–
12.	13.32	*o*-Eugenol	–	0.6	0.3	0.8	–
13.	13.72	tα-Cubebene	1.9	–	–	–	0.5
14.	13.95	tβ-Elemene	3.9	1.7	–	–	–
15.	14.39	tCaryophyllene	–	–	–	–	2.2
16.	14.50	t4,8,8-Trimethyl-2-methylene-4-vinylbicyclo[5.2.0]nonane,		2.4	–	0.5	–
17.	14.62	t2-Isopropyl-5-methyl-9-methylene-bicyclo[4.4.0]dec-1-ene	1.2	–	–	–	1.7
18.	14.69	tAlloaromadendrene	–	–	–	–	0.2
19.	14.94	Geranylacetone	1.5	–	–	–	0.5
20.	15.00	2,6-Diaminopyridine	–	–	2.3	–	–
21.	15.04	tα-Humulene	2.8	–	–	–	–
22.	15.04	tβ-Gurjunene	–	–	–	–	0.2
23.	15.25	tα-Amorphene	–	–	–	–	0.6
24.	15.32	tγ-Muurolene	–	0.6	–	–	–
25.	15.40	tβ-Cubebene	–	–	–	1.1	–
26.	15.44	tGermacrene D	11	6.5	–	–	–
27.	15.54	β-Ionone	–	–	–	–	2.3
28.	15.68	tBicyclogermacrene	3.6	3.8	–	–	–
29.	15.70	tδ-Guaiene	–	–	–	–	0.3
30.	16.08	tδ-Cadinene	2.3	1.4	0.5	0.6	1.1
31	16.41	otElemol	–	–	2.1	1.1	2.8

Table 1 – (continued)

S/No	R_T/ min	Compound	Percentage of total				
			1st h	2nd h	3rd h	4th h	4 h
32.	16.89	[ot](−)-Spathulenol	–	–	–	1.3	–
33.	16.99	[ot]Caryophyllene oxide	–	–	0.4	–	1.1
34.	17.16	[ot](+)-Spathulenol	3.4	4.7	1.4	–	2.7
35.	17.16	[ot]Guaiol	2.6	1.4	0.5	–	–
36.	17.22	1,12-Dodecanediol	–	–	–	0.6	–
37.	17.23	*trans*-2-Dodecen-1-ol	–	–	0.9	–	0.8
38.	17.67	[ot]γ-Eudesmol	–	–	0.5	–	–
39.	17.95	[ot]β-Eudesmol	–	–	–	0.9	–
40.	18.02	[t]γ-Gurjunene	–	–	4.9	–	3.4
41.	18.04	[t]α-Gurjunene	1.8	7.2	–	–	–
42.	18.12	Cyclotetradecane	–	–	–	0.3	–
43	18.14	[t]α-Elemene	6.3			2.5	–
44.	18.14	Cyclodecane	–	–	1.0	–	–
45.	18.53	Tetradecanal	5.1	–	1.6	–	–
46.	18.65	Pentadecanal	–	–	–	–	6.9
47.	18.71	(*E*)-2-Tridecen-1-ol	–	–	–	6.5	–
48.	18.73	11-Tetradecyn-1-ol-acetate	–	–	5.9	–	–
49.	18.76	1,13-Tridecanediol diacetate	-	7.9	–	–	–
50.	19.46	1-Hexadecanol					0.7
51.	19.51	Benzyl Benzoate	0.6	0.7	0.7	0.5	0.6
52.	19.52	1,13-Tetradecadiene	–	–	–	1.5	–
53.	19.73	*cis*,*cis*,*cis*-7,10,13-Hexadecatrienal	–	–	1.0	–	–
54.	20.01	18-Nonadecen-1-ol	–	–	0.5	–	–
55.	20.47	Hexahydrofarnesyl acetone	2.1	4.4	5.1	5.0	4.8
56.	20.51	(*Z*)6, (*Z*)9-Pentadecadien-1-ol	–	–	0.3	–	–
57.	20.71	[fa]Pentadecanoic acid	–	–	0.8	–	–
58.	20.86	1,4-Ecosadiene	–	–	0.8	–	–
59.	20.99	*cis*,*cis*-7,10-Hexadecadienal	–	–	–	5.3	–
60.	21.12	[usfa]α-Linolenic acid	–	–	5.6	6.8	–
61.	21.61	[ot]3,5,11,15-tetramethyl hexadec-1-en-3-ol-	–	–	–	–	1.0
62.	21.70	[ot]Isophytol	–	–	2.3	–	–
63.	21.93	[fa]*n*-Hexadecanoic acid	–	0.5	0.7	8.9	3.1
64.	22.48	[t]Kaur-15-ene	–	–	0.2	–	–
65.	22.76	(13*S*)-8,13-epoxy-labd-14-ene	–	6.4	7.2	6.9	2.4
66.	22.98	[t]Kaurene	–	–	–	–	0.8
67.	23.08	[t]Kaur-16-ene	1.7	2.2	2.6	2.3	–
68.	23.41	[fame]Linoleic acid methyl ester			0.7		
69.	23.41	[usfa]Linoleic acid	–	–	–	0.7	–
70.	23.48	[fame]Oleic acid, methyl ester	–	–	1.1	1.6	–
71.	23.70	[ot]Phytol	2.8	7.6	7.2	8.9	19.7
72.	23.89	[usfa]Linoleic acid	–	–	–	0.4	–
73.	23.89	[usfa]Oleic acid				1.7	
74.	23.93	[(2,4,6-Triethylbenzoyl)thio]-acetic acid	–	–	1.4		–

Table 1 – (continued)

S/No	R_T/min	Compound	Percentage of total				
			1st h	2nd h	3rd h	4th h	4 h
75.	24.22	[fa]Octadecanoic acid	–	–	1.2	0.9	–
76.	25.30	[ot]Kauran-16-ol	–	1.1	–	–	0.3
77.	25.33	[ot]16.β.H-Kauran-16-ol	–	–	2.4	–	–
78.	25.50	1,2-Benzisothiazole,3-(hexahydro-1H-azepin-1-yl)-,1,1-dioxide	–	–	–	–	0.8
79.	27.62	1-Iodooctadecane	–	–	0.3	–	0.1
80.	31.17	9-Butyldocosane	–	–	–	–	0.2
		Total	67.8	63.9	64.4	67.0	66.3

Key: t = terpene, ot = oxygenated terpene, fa = fatty acid, usfa = unsaturated fatty acid, fame = fatty acid methyl ester.

Sabinene is a monoterpene and is the subject of several patents. Monoterpenes have been found to exhibit several pharmacological properties, including antifungal, antibacterial, antioxidant, anticancer, and antispasmodic activities.[16] This constituent, when incorporated in some compounds, has been found to have great medicinal potentials. When it occurs in natural compounds, its possible roles can thus be considered. For example, it is useful in the enhancement of activity of antibiotics. Oxazolidinone antibiotics are known to be active against multi-drug resistant Gram-positive organisms. They are not cross-resistant with other antibiotics.[17–18] In an invention, oxazolidinones having a bicyclic[3.1.0] hexane-containing moiety were found to be effective against aerobic, anaerobic pathogens including multi-resistant staphylococci, streptococci, and enterococci, bacteroides species, clostridia species as well as acid–fast organisms, such as *Mycobacterium tuberculosis* and other mycobacterium species which are implicated in leprosy.[19] A study based on the work of *Basile et al.*[20] and *Skolnick et al.*[21] provides novel 1-heteroaryl-3-azabicyclo[3.1.0] hexanes and similar processes and intermediates for synthesizing such compounds and compositions and methods using the compounds for the treatment or prevention of central nervous system (CNS) disorders, including depression and anxiety. Some experiments[22] based on studies carried out by *P. Skolnick et al.*[23] and *M. Briley*[24] showed that phenyl substituted-3-azabicyclo[3.1.0] hexanes inhibited the reuptake of biogenic amines that serve as neurotransmitters in the CNS. Therefore, compounds which inhibit the reuptake of these neurotransmitters may be useful as antipsychotic agents, effective in treating CNS disorders, including drug dependency. Bicyclic compounds have also been reported to be nicotinic acetylcholine receptor inhibitors, and have been found useful for the treatment of clinical conditions, such as anxiety, Alzheimer disease, depression, convulsive disorders, cognitive memory disorders, Attention Deficient Disorder/Hyperactivity Syndrome, inflammation, pain, psychosis, mania, Parkinson's disease, sleep disorders, and disorders of the CNS related to or affected by certain nicotinic receptors.[25–29] These bicyclic [3.1.0] hexane-containing moiety and derivatives have not been reported present in any extract of *A. cissampeloides,* but the presence of this constituent in the essential oil suggests the potential of the plant for the management of nervous disorder, stress, venereal diseases, and leprosy.[7,8]

β-Linalool is a terpene alcohol. In a review article, it was reported that monoterpenes have been found to exhibit significant effects on the cardiovascular system[30] in addition to those listed previously.[16] In a study on the effect of the optical isomers of linalool on human subjects, it was observed that while (+)-linalool exhibited stimulating effect on the cardiovascular system, (−)-linalool exhibited a depressing effect.[31] Linalool is usually found in the racemic form in nature. (±)-Linalool has been reported to induce hypotension associated with tachycardia in rats.[32] Thus, this constituent may cause the reduced systolic blood pressure observed in hypertensive human subjects who were treated with herbal preparations of the plant.[11] Several patents have been filed on the various applications of linalool. One of such is on the control of ticks and fleas with linalool.[33] The patent is based on a report on the inhibition of houseflies by certain terpenoids.[34] Thus, *A. cissampeloides* may function as a broad-based insecticide not limited to scabies. This constituent is also present as the major volatile constituent (15.6 %), of *Thea viridis*, green tea,[35] and in the essential oil of the oleo-gum resin of Frankincense, Boswellia species (6.64 %), which has been identified for its immune-enhancing, antibacterial, antifungal, antiviral, antiseptic, wound healing, anti-inflammatory, and anti-cancer properties.[36] Some of these bioactivities may be exhibited by *A. cissampeloides*.

F. Mondello et al.[37] established the efficacy of terpinen-4-ol, the main component (30 % minimum) of *Melaleuca alternifolia* Cheel (tea tree oil), against human pathogenic *Candida* species which were azole-susceptible and -resistant. The susceptibility of *Legionella pneumophila*, one of the microorganisms implicated in Legionnaire's disease, to *M. alternifolia* oil, was also reported.[38] These studies[37,38] formed the basis of a patent[39] which refers to the use of terpinen-4-ol, both aqueous solution and vapour forms as antimicrobial agent against bacteria of *Legionella genus*, preferably *L. pneumophila* for disinfecting systems for the distribution of water in various facilities. Terpinen-4-ol is reported to be the major constituent of the essential oil from *Alpinia zerumbet* or *Alpinia speciosa* (Blume) D. Dietr, which is widely used as a tea in the management of arterial hypertension in alternative medicine.[30] *S. Lahlou et al.*[40,41] reported the cardiovascular and antihypertensive effects of terpinen-4-ol, and concluded that the hypotensive effects of the essential oil are partially attributed to the actions of terpinen-4-ol. Thus, this constituent has antihypertensive

activity and may contribute to the observed antihypertensive activity of *A. cissampeloides*.[11]

Azulene has been recognized for its soothing effect, anti-inflammatory activity, and several medicinal applications. Its anti-inflammatory activity has been demonstrated in several animal models.[42] A derivative, chamazulene carboxylic acid, is a natural profen with anti-inflammatory activity.[43]

α-Terpineol is irritating to eyes, respiratory system, and skin. It constitutes 0.3 % of the essential oil sample collected over a period of four hours. α-Terpineol has been reported to exhibit a hypotensive effect in rats and also induce vasorelaxation.[44,45] These two effects have been confirmed and possible pathways proposed for the effects.[46] α-Terpineol has been reported to exhibit antioxidant, antiseptic, anti-hypernociceptive and anti-inflammatory activity[47,48], and may confer some of these bioactivities on the plant essential oil.

(−)-Myrtenol, a bicyclic monoterpene alcohol, has been reported to exhibit hypotensive effects at doses of l mg kg^{-1} when administered intravenously in rats.[44] It may function in a similar manner in human subjects.

Indole is a precursor to many pharmaceutical products, and the indole core is commonly found in several varieties of biologically active compounds.[49] Indole structures are able to bind many receptors in the body and hence are considered privileged structure motifs.[50] Thus, a great deal of research has been dedicated to incorporate indole in the synthesis of new anti-mitotic compounds for the treatment of cancer. One of such compounds, 5-methoxy-1-(3,4,5-trimethylphenyl)-1-H-indole, is described as having possible anti-mitotic properties.[51] Aromatic ethers derived from indole have been synthesized and found useful for the treatment of diseases linked to the dysfunction of 5HT1-like receptors.[52] 5-hydroxytryptamine (5HT), commonly called serotonin, is proposed to play an important role in various pathological conditions, such as psychiatric disorders, including anxiety, depression, aggressiveness, panic attacks, obsessive compulsive disorders, schizophrenia, suicidal tendency, and some neurodegenerative disorders, including Alzheimer's disease, Parkinsonism, as well as other health disorders, such as migraine, cephalalgia and those linked to alcoholism.[53–58] Most of the compounds synthesized are potent agonists of 5HT1-like receptors, and are used for the treatment of migraine and vasospatic disorders.[59–64] 3,5-Substituted indole has been found useful in the control of visceral pain which may be caused by disease or injury to some internal organs. Examples of visceral pains managed by such compounds include inflammatory bowel syndrome, pancreatitis, diverticulitis, Crohn's disease, peritonitis, gastroenteritis, endometriosis, dysmenorrheal interstitial cystitis, dyspepsia, renal colic or biliary colic.[65] These indole derivatives have not been reported present in any extract of *A. cissampeloides,* but the occurrence of indole in the essential oil may contribute to the use of the plant isolate for the management of nervous disorders in alternative medicine.[7]

γ-Elemene has been reported present in appreciable quantity in the leaf essential oil samples of *Murraya microphylla* and *Murraya alata*. Caryophyllene, present in the essential oil from *A. cissampeloides,* is also present in the essential oil of *M. microphylla*. The essential oil from the two Muraya species have been shown to exhibit antibacterial and antioxidant properties.[66] Thus, γ-elemene and caryophllene may contribute to the antibacterial activity of herbal preparations from *A. cissampeloides*.[7]

2,5,5-Trimethyl-1,3,6-hepatriene is an alkene, and has been reported to be a constituent of the essential oil of *Salvia bertolonii* Vis and *Salvia pratensis* L. *S. pratensis* is used as a bactericidal agent for ulcers, wound healing, sore throat, and influenza.[67]

Camphene, a bicyclic monoterpene, is a constituent of many plant essential oils. It is non-toxic and is used as food additive, for artificial flavouring, and in fragrances, as well as in the manufacture of synthetic camphor and insecticides. It has been found to reduce plasma cholesterol and triglycerides in hyperlipidemic rats.[68] Accumulation of lipids, plasma cholesterol and triglycerides within the blood vessels of the artery is central to the development of atherosclerosis and coronary heart disease [69–71]. In a study, it was found that lipid-lowering therapy is effective in reducing cardiovascular mortality and morbidity in people with peripheral arterial disease, and statin is the recommended drug.[72] However, some patients do not tolerate statin, while for some, using statin treatment alone does not achieve the desirable lipid level. Thus, there is need to investigate other possible compounds, including those of plant origin, with the same cholesterol-lowering effect.[68] The hypolipidemic property of the essential oil from Chios mastic gum, MGO, a resin produced by the plant *Pistacia lentiscus* var. Chia,[73] was evaluated in rats in which hyperlipidemia was detergent-induced. Treatment of HepG←2 cells with camphene led to a decrease in cellular cholesterol content to the same level as mevinolin, a potential lipid-lowering drug and a well-established 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. The hypolipidemic activity of MGO was unequivocally attributed to camphene, a minor constituent (0.8 %) of the essential oil. However, synergistic action between camphene and other MGO components was observed. Camphene did not exhibit cytotoxicity in human hepatic cells and may be developed as an alternative lipid-lowering agent.[68] In a study on some plant-derived antioxidants, geraniol and camphene were found to offer significant protection against reactive oxidation species. The results from the study indicated the pharmacological potential of the two compounds in the management of lung inflammatory diseases which arise from oxidative stress.[74] Camphene (3.7 %) was found present in the 1st hour essential oil fraction of *A. cissampeloides,* and may contribute to the observed antihypertensive action of the plant extract in clinical trials[11] as well as to its use in the management of bronchitis and lung ailments in alternative medicine.[8]

o-Eugenol is one of the terpenoid compounds found to exhibit muscle relaxant, anaesthetic and inhibitory effect on locomotion. Methyl eugenol and cineol also exhibited similar effects.[75] The sedative effects and motor impairment activity of the root extract of *Ferula gummosa* have been proposed to be caused by these terpenoid compounds.[76] Thus, *o*-eugenol may be responsible for the use of *A. cissampeloides* in the management of stress and nervous disorders.[7]

α-Cubebene is one of the sesquiterpenes derived from the fruit of the Osage tree, *Maclura pomifera*. In some studies, the constituent sesquiterpenes, singly or in combination, were reported to exhibit excellent repellency against arthropods, such as cockroaches, mosquitoes, mites, ticks, and spiders.[77] Several of these constituents performed better than the commercial standard *N*,*N*-diethyl-3-methylbenzamide (DEET) against female German cockroaches and are contained in a patent. These reports are the basis of a patent on repellents obtained from terpenoids for use against arthropods.[78] These repellents are less toxic than *N*,*N*-diethyl-1,3-methylbenzamide, (DEET), which has been reported to cause severe adverse health effects.[79,80] α-Cubebene may thus increase the insecticidal activity of *A. cissampeloides*.[8] This constituent has also been found to be the major constituent in the volatile oil from the peel and flesh of *Garcinia mangostana*, L. with relative contents of 32 % and 41 %, respectively,[81] and an extract of the plant has been found to offer protective effects against induced cytotoxic changes and increased level of reactive oxygen species, and it has been suggested that the extract may prevent or decrease the severity of Alzheimer disease.[82] It is possible that α-cubebene may contribute to the effectiveness of *A. cissampeloides* in the management of nervous disorders in alternative medicine and may also enhance the insecticidal activity of the plant.[8]

β-Elemene is present in the 1st and 2nd hour fractions. It is a constituent of *Piper nigrum* which has been found to exhibit insecticidal activity, and is also employed in alternative medicine in the management of haemorrhoids, cold, congestion, dyspepsia, vomiting, and diarrhea.[83]

Caryophyllene, also known as β-caryophyllene, is a bicyclic sesquiterpene present in essential oils of many plants and has several medicinal properties. These include anti-inflammatory, anti-carcinogenic, antioxidant, antimicrobial, and analgesic properties.[84] In a study, β-caryophyllene was found to increase paclitaxel activity by ten-fold, thus potentiating the anti-cancer activity of paclitaxel on some human tumour lines, suggesting that β-caryophyllene facilitates the passage of paclitaxel through the cell membrane.[85] Caryophyllene is present in appreciable quantities in *Cannabis sativa* (3.8–37.5 %). A cannabis extract, sativex, is used in Canada for the treatment of neuropathic pain in multiple sclerosis, and because (*E*)-β-caryophyllene is a significant constituent in cannabis essential oil and shows significant cannabimimetic effects, it is proposed that it may contribute to the overall effect of cannabis medications. Caryophyllene has thus been declared to potentially modulate inflammatory and other pathophysiological processes.[86] It is also a constituent of essential oils (51.8–57.6 %) obtained from the dried fruits of *Piper guineense*[87] commonly used for the management of mental illness, impotence, hypertension, and as antimicrobial in the practice of alternative medicine in Nigeria[88], and was also found to exhibit hepatoprotective effect.[89] Caryophyllene has also been demonstrated to be potentially useful in the prevention and treatment of colitis.[90] In a study on the anti-tumour properties of the volatile oil from *Zanthoxylum rhoifolium* Lam leaves and some terpenes including β-caryophyllene *in vitro* and *in vivo*, it was concluded that the volatile oil exhibited efficient anti-tumour activity and significant immunomodulatory action *in vivo*, which may be attributed to β-caryophyllene associated to the synergism of other natural compounds present in the volatile oil.[91] The listed bioactivities of β-caryophellene may also be expected to be present in preparations of *A. cissampeloides*.

Caryophyllene oxide has been reported to be anti-inflammatory as well as acting as peripheral analgesic, and exhibiting activity against *C. albicans* and repellence against *Anopheles gambiae*, a malaria vector.[92] It has also been proposed as a potential therapeutic compound for the prevention and treatment of cancer.[93] It has been found to exhibit sedative effect on silver catfish.[94] Studies on *Satureja parnassica* oil, which is very rich in caryophyllene oxide, has been found to show moderate antibacterial activity against *Helicobacter pylori*.[95] Thus, caryophyllene oxide may contribute to the bioactivity of *A. cissampeloides* as an antimicrobial and an analgesic for headache and back pain as claimed in alternative medicine.[8]

4,8,8-Trimethyl-2-methylene-4-vinylbicyclo[5.2.0]nonane has been found to be a constituent (12 %) of the volatile oils from *Fusarium trincinctum,* an endophytic fungus which showed antimicrobial activity against eight bacteria and two fungi.[96]

2-Isopropyl-5-methyl-9-methylene-bicyclo[4.4.0]dec-1-ene is reported present in the essential oil from chocolate mint (2.75 %), which was observed to possess scavenging NO radical activity as well as anti-inflammatory activity.[97]

Alloaromadendrene and caryophyllene, both present in the essential oils from *A. cissampeloides* have been found present in the essential oil from the leaves of *Psidium guajava*,[98] which have been reported to exhibit antibacterial property and were efficacious in the management of diarrhea, dysentery, and gastroenteritis.[99]

Geranyl acetone has been reported present in the leaf essential oil obtained from *S. radiatum*, a pro-fertility medicinal plant[2], and also in the rhizome of two types of *Curcuma longa* grown in Bangladesh and used in the management of jaundice, liver ailments, ulcers, parasitic infections, and skin diseases.[100] The compound has also been reported as a constituent of volatile organic compounds in normal skin area in a study on analytical profiling of chronic wounds.[101]

α-Humulene has been isolated from the essential oil of *Cordia verbenacea* and was found to produce anti-inflammatory effects comparable to those observed in dexamethasone-treated animals.[102] This constituent may be useful in the management of pain arising from inflammation, and may be responsible for this bioactivity of *A. cissampeloides*.

α-Amorphene, a sesquiterpene, and some other constituents in the essential oil from *A. cissampeloides*, including α-terpineol, camphene, β-elemene, caryophyllene, α-humulene, γ-muurolene, δ-cadinene (−)-spathulenol, and caryophyllene oxide have been reported present in the flower essential oil of *Magnolia liliflora,* which has been found effective in the management of decubitus ulcer in nursing pregnant women.[103] It is possible that the leaf essential oil from *A. cissampeloides* may exhibit such bioactivity. This finding is relevant to the use of preparations from *A. cissampeloides* in the treatment of wounds and sores.

γ-Muurolene, a sesquiterpene, and other constituents, namely, terpinen-4-ol, β-elemene, α-amorphene, δ-cadinene, and *n*-hexadecanoic acid, all present in the essential oil from *A. cissampeloides,* have been reported present in the essential oil obtained from *Radix Linderae,* which has been found useful in preventing the occurrence of decubitus in aged people.[104] This observation may lead to the expectation that *A. cissampeloides* and *R. Linderae* essential oils may have some bioactivities in common.

Germacrene D, an anti-mosquito compound,[105] has been found present in the ethanol extracts of the leaves of *Vitex negundo* L. Other compounds present in the extract, which are also present in the essential oils from *A. cissampeloides,* include β-elemene, caryophyllene oxide, (+)-spathulenol, α-linolenic acid, *n*-hexadecanoic acid, phytol, and octadecanoic acid. The ethanol leaf extract of *V. negundo* was observed to possess remarkable larvicidal, oviposition deterrent and repellent activity against hazardous mosquitoes, namely *Aedes aegypti, Anopheles stephensi,* and *Culex quinquefasciatus*.[106] Thus, some bioactivities, especially repellence activity may be observed in *A. cissampeloides*.

β-Ionone is a constituent of a formulation for exterminating lice and lice eggs. The formulation consists of one or more terpenes, namely, limonene, β-ionone, linalool, geraniol, myrcene, and carvone. β-Ionone has antibacterial and antifungal properties.[107] Thus, the essential oil form *A. cissampeloides* may be expected to exhibit antimicrobial activity as well as these insecticidal properties.

Bicyclogermacrene has been reported present in the essential oil from the fresh leaves of *Piper cernuum* and *Piper regnellii*. Other constituents present in both *P. regnellii* and essential oils from the leaves of *A. cissampeloides* include linalool, α-terpineol, β-caryophyllene, α-humulene, spathulenol, and caryophyllene oxide. The essential oils obtained from *P. cernuum* and *P. regnellii* were observed to display significant activities against *Staphylococcus aureus* and *Candida albicans*.[108] This antimicrobial activity may be expected to be observed in the essential oils from *A. cissampeloides*.

δ-Cadinene is present in all the fractions. It has been identified as one of the major components in the essential oil from the peel of orange fruit, *Citrus sinensis*. The essential oil of *C. sinensis* exhibited antimicrobial activity against some Gram-positive and Gram-negative bacteria as well as *Candida* strains.[109]

(+)- and (−)-spathulenol, β-caryophyllene, and caryophyllene oxide, all present in the essential oils of *A. cissampeloides,* have also been reported present in the leaf essential oil of *Stevia rebaudiana,* and these constituents have been demonstrated to partially account for the antimicrobial activity of the aqueous leaf extract of *S. rebaudiana*.[110] Extracts from the plant have been found to act as a hypotensive regulator and also observed to possess hypoglycemic, antimicrobial, and contraceptive activities. Caryophyllene oxide and spathulenol constituted 43 % of essential oil from leaves of *S. rebaudiana* from Brazil.[111] These two constituents identified in *Salvia sclarea* oil were found to be active against *S. aureus*.[112] The essential oil obtained from *Salvia elegans* Vahl, was found to contain spathulenol and caryophyllene as the major components, and was reported to exhibit excellent inhibitory larvicidal effect against *Aedes albopictus,* a mosquito vector.[113] This bioactivity may be exhibited by *A. cissampeloides*.

(+)-Spathulenol, (−)-guaiol, and caryophyllene oxide were the isolated compounds from the essential oil of *Aloysia gratissima* responsible for anaesthetic induction in silver catfish. Spathulenol showed potent sedative and anaesthetic activities in silver catfish, and was proposed as a viable compound for the development of a new anaesthetic.[94]

Guaiol has been found present in the essential oil of *Teucrium polium* L. and was reported to inhibit the intestinal motility of the isolated rabbit jejunum. Crystalline isolation and physicochemical characterization has identified guaiol as a major constituent of an active spasmolytic fraction of the essential oil of *T. polium* L.[114] Guaiol was found to exhibit sedative effect on silver catfish.[94] Thus, the essential oil from *A. cissampeloides* leaves may exhibit anaesthetic effect.

α-Gurjunene and elemol both present in the essential oil from *A. cissampeloides* have been found present in the volatile components in *Rhizome Zingibers*, *Zingiber Officinale Roscoe,* and *Ginger Pee* which are used in Chinese traditional medicine for rheumatism, cold, stomach pain, and diarrhea.[115]

Benzyl benzoate emulsion was reported in 1946 as a very effective miticide in the management of scabies, and when incorporated at 68 % v/v into a mixture of dichlorodiphenyltrichloroethane, DDT (6 %), benzocaine (12 %), and Tween 80 (14 %), was found to be miticidal, larvicidal, lousicidal, ovicidal and antipruritic. DDT is ineffective against human scabies.[116] This constituent may contribute to the effectiveness of the leaves of *A. cissampeloides* in the management of scabies.

Cis,*cis*,*cis*-7,10,13-Hexadecatrienal is one of the major constituents in the methanol leaf extract of *Lantana camara,* which was found to have larvicidal effect on some species of mosquitoes. Other constituents present in the extract, which are also found in the essential oils from *A. cissampeloides,* include oleic acid, hexadecanoic acid, and phytol.[117] *n*-Hexadecanoic acid, present in the essential oils from both plants, has been reported as a potent mosquito larvicide.[118] Thus, the essential oils from the leaves of *A. cissampeloides* may function as a mosquito larvicide.

Hexahydrofarnesyl acetone is present in all the hourly fractions as well the 4-hour sample. It has been reported present in appreciable concentration in the essential oil obtained from the leaves of *C. procera* (Ait.) R. Br. The insecticidal potential and possible role in malaria control was discussed.[5] It is the oxidation product of phytol[119] and some of this constituent may actually be present as phytol in the native plant material prior to hydrodistillation.

Cis,*cis*-7,10-Hexadecadienal has been reported present as one of the major constituents in the essential oil obtained from the leaves and stem of *Euphorbia heterophylla*, a medicinal plant used traditionally in the management of gonorrhoea, respiratory tract infection, and warts, and found

effective as a fish poison and insecticide. It has also been shown to exhibit some antimicrobial and anti-inflammatory properties. Other constituents common to the essential oils of *E. heterophylla* and *A. cissampeloides* include linoleic acid, phytol, oleic acid, and octadecanoic acid.[120]

Isophytol has been reported to be very toxic to aquatic life with very long lasting effects, and is suspected of damaging fertility or human foetus. It is also reported to irritate the eyes, skin, and respiratory system.[121] Isophytol in the essential oil may be an abortifacient.

Phytol has been found present in some medicinal plants used in the management of asthma in alternative medicine. These include essential oils from the leaves of *C. procera*[5] and *E. hirta*.[4] The anti-inflammatory property of phytol as well as its reactive oxygen species-promoting property and its bioactivity in long suppression of arthritis[6] was suggested as being responsible for the possible response of asthmatic patients when these extracts are employed in alternative medicine. The appreciable quantity of phytol in the essential oil of *A. cissampeloides* may be suggestive of a possible role of the plant in the effective management of arthritis and asthma. Phytol has been identified as a major component in the ethyl acetate-soluble fraction obtained from the methanolic extract of the leaves of *Pereskia bleo*, a medicinal plant alleged to have anti-cancer, anti-tumour, anti-rheumatic, anti-ulcer, and anti-inflammatory properties. It is also used for the relief of gastric pain. In a study of the cytotoxic activity of the plant[122], it was found that the ethyl acetate fraction exhibited high cytotoxic activity against human nasopharyngeal epidermoid carcinoma cell line and lower toxicity against human colon carcinoma cell line and hormone-dependent breast carcinoma cell line. It was proposed by the authors that phyto1, which has been found to show significant anti-tumour activity against mouse lymphocytes leukaemia cells, lymphoid leukaemia cells, human colon cancer cells, and gastric cancer cells, was responsible for the reported bioactivity of the plant. This suggests that the essential oils from *A. cissampeloides* may exhibit some anti-cancer and anti-tumour activity due to the presence of phytol. Phytol has also been reported to be a tumour promoter on l CR mouse skin.[123] Phytol and derivatives are the subject of a patent claiming that these compounds can serve as active ingredients in medicaments to lower serum levels of triglycerides and/or cholesterol, and can be administered to patients with disease conditions, such as type II diabetes, obesity or patients with cardiovascular disease.[124] These findings may also explain the anti-hypertensive activity of *A. cissampeloides,* and suggest the usefulness of the plant in the management of type II diabetes and obesity.

The essential oils contain five kaurene derivatives, namely, kaurene-15-ene, kaurene-16-ene, kaurene, kauran-16-ol, and 16 .β. H-kauran-16-ol. Kaurane diterpenes, including (−)-*ent*-kaur-16-en-19-oic acid, (−)-kaur-16-en-19-ol, and (−)-kauran-16-α-o1, have been reported to be effective against trypomestigotes of *Trypanosome cruzi*, a parasitic protozoan capable of causing life-threatening infections and cardiac complications.[125] Natural stevioside has a kaurene skeleton as aglycone. It has been shown that it can lower blood sugar[126] and blood pressure.[127] In animal studies, it has been shown to be a diuretic and was also found to stimulate the secretion of insulin.[128] Medicaments incorporating kaurene structure have been patented for the treatment of non-insulin dependent diabetes mellitus and hypertension[129], and also for treating and preventing coronary heart disease, cerebral apoplexy, cerebral ischemia, and rhythm disturbance.[130] These reports suggest possible medicinal applications of *A. cissampeloides*.

The saturated fatty acids in the essential oils are pentadecanoic acid, *n*-hexadecanoic acid, and octadecanoic acid, while the unsaturated fatty acids are α-linolenic acid, linoleic acid, and oleic acid. *n*-Hexadecanoic acid and α-linolenic acid are present in appreciable quantities compared to the other fatty acids. Fatty acids are reported to exhibit antibacterial and antifungal properties.[131,132] *n*-Hexadecanoic acid inhibits phospholipase A2 which hydrolyses ester bonds and initiates steps resulting in inflammation which can lead to pathological conditions of rheumatoid arthritis, bronchial asthma, ulcerative colitis, psoriasis, and Crohn's disease.[133] The anti-inflammatory property of *n*-hexadecanoic acid, including structural evidence and kinetic measurements, has been reported[133] and the authors proposed that the results validate the rigorous use of oils rich in hexadecanoic acid for the treatment of rheumatic systems. This fatty acid is also reported to be hypocholesterolemic, nematicidal, pesticidal, and functions as an antioxidant, anti-androgenic flavour and 5-α-reductase inhibitor[134] and a potent mosquito larvicide.[118] Octadecanoic acid exhibits antimicrobial activity.[118] Linoleic acid methyl ester exhibits anti-cancer activity.[135] Oleic acid exhibits antibacterial activity[136], while α-linolenic acid exhibits higher anti-inflammatory activity than docosahexaenoic acid.[137] The occurrence of these fatty acids in the essential oils from *A. cissampeloides* may render the plant effective in the management of diseases which arise from inflammation; these include bronchial asthma and arthritis. These fatty acids also support the antimicrobial activity of the plant, and suggest its potential as anti-cancer agent and mosquito larvicide.

Analysis of the hourly fractions of the essential oils revealed the occurrence of some constituents that were not detected in the conventional 4-hour collection. These results are a guide to the fractions that are rich in certain constituents. For example, azulene, caryophellene, and phytol are found largely in the 4-hour collection, while (−)-myrtenol, camphene, β-elemene, and α-humulene are predominant in the first hour fraction.

4. Conclusion

The results from this study show that several constituents of the essential oils have potentials as medicaments in the management of hypertension, nervous disorders, headache, pain, and leprosy. Insecticidal potential is also proposed. Some of the constituents, such as phytol, (13*S*)-8,13-epoxy-labd-14-ene, *n*-hexadecanoic acid, 1,13-tridecanediol diacetate, α-gurjunene, and germacrene D can be isolated from the essential oils and their bioactivities investigated. The effects of climate, soil, drying conditions, and methods of isolation of the essential oils on the constituents should also be investigated.

ACKNOWLEDGEMENTS

The authors express appreciation to Mr. S. K. Odewo for his advice on plant selection and authentication, Mrs. J. O. Olafimihan, Chief technologist, Mr. Dan Achem and Mr. Mejida, technologists of the University Central Research Laboratory for assistance with the GC-MS, and to the University of Lagos for the facilities and reagents.

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SAŽETAK

Potencijal sastojaka esencijalnog ulja iz lišća biljke *Adenia cissampeloides* za primjenu u medicini i kao pesticida

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Adenia cissampeloides (Panch. ex. Hook.) Harms je biljka koja se u alternativnoj medicini primarno upotrebljava za ublažavanje hipertenzije i nekoliko drugih bolesti. Provedena je izolacija i GC-MS analiza pet esencijalnih ulja frakcijski izdvojenih za vrijeme hidrodestilacije osušenog lišća koja je trajala preko četiri sata. Ulja su sadržavala fitol, α-linolensku kiselinu, *n*-heksadekanoičnu kiselinu, heksahidrofarnezil aceton, (13*S*)-8,13-epoksi-labd-14-en, kaur-16-en, gvajol, α-gurjunen i α-elemen. Provedena je rasprava i o nekoliko različitih bioaktivnosti sastojaka kao i o njihovoj potencijalnoj primjeni u medicini, farmaciji i industriji pesticida. Sastojci izolirani iz *A. cissampeloides* postoje i u esencijalnim uljima nekih drugih biljaka. Bioaktivnosti takvih biljaka upućuju na to da postoje i druge moguće primjene *A. cissampeloides*.

Ključne riječi
Adenia cissampeloides, GC-MS, ljekovito bilje, esencijalna ulja, bioaktivnost

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Pregledni rad
Prispjelo 28. travnja 2018.
Prihvaćeno 20. srpnja 2018.