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Review article

Ouratea genus: chemical and pharmacological aspects

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ABSTRACT

Ouratea and the other genera of the Ochnaceae family are a rich source of flavonoids and biflavonoids. These can be used as chemotaxonomic markers of *Ouratea*. Some biflavonoids, as well as extracts of the *Ouratea* species show important biological activities, such as anti-tumour, antiviral, vasodilation, antimicrobial and DNA topoisomerase inhibition. On the other hand species of this genus are used in folk medicine for gastric distress, dysentery, and diarrhea; as an astringent, a tonic, and for the treatment of inflammation-related diseases. The information collected in this review attempts to summarise the phytochemical and biological activities studied in *Ouratea* species that may be helpful to guide researches, to undertake further investigation concerning the common properties of *Ouratea* species and evaluation as a source of active compounds.

Introduction

The Ochnaceae family comprises 27 genera and 600 tropical species distributed in tropical and subtropical zones throughout the world (Amaral, 1991). *Ouratea* is the largest genus of this family and comprises approximately 300 tropical species appearing mainly in South America and tropical Africa (Heywood, 1978; Dahlgren, 1980). Among these species, 120 are endemic to the Neotropical zone (Sastre, 1988; Salvador et al., 2010) along 28 species recently described (Sastre, 1995; 1997; 2001; 2004; 2005; 2006; 2007; Yamamoto, 1995; Salvador et al., 2006). The species are evergreen trees, shrubs, and shrublets (Chacon, 2011; Carvalho et al., 2000).

The Ochnaceae family has been characterized as a major source of biflavonoids and up to now it has been best represented by the *Lophira* (Ghogomu et al., 1989; 1990; Tih et al., 1999; 2006), *Luxemburgia* (Oliveira et al., 2002; Carvalho et al., 2004), Ochna (Anuradha et al., 2006; Bandi et al., 2012) and *Ouratea* (Velandia et al., 2002; Fidelis et al., 2012) genera.

The biflavonoids of the *Ouratea* genus are found as flavone-chalcone dimers, and rarely biisoflavone, and can be used as chemotaxonomic markers of genus. Besides the flavonoids and biflavonoids, several metabolites have been isolated from this genus such as lignans, triterpenes, diterpenes, steroids, monosaccharides, depsides, and triacylglicerides (Suzart et al., 2007a). *Ouratea* species are used in folk medicine to treat gastric distress, dysentery, and diarrhoea (Mbing et al., 2006); as an astringent, and tonic (Estevam et al., 2005), as well as for the treatment of inflammation-related diseases such as rheumatism, sprains and arthritic disorders (Carbonari et al., 2006). Furthermore, scientific studies have revealed important biological activities of biflavonoids and extracts of *Ouratea*,

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such as anti-tumour, antiviral and antimicrobial activities among other pharmacological activities (Suzart et al., 2007a), but not all have a popular use. Hence, *Ouratea* species have been investigated biologically, but some ethnopharmacological effects remain undetermined.

In this review, all isolated constituents will be analysed based on their biological activities, however the traditional uses will be considered.www

Ethnopharmacology

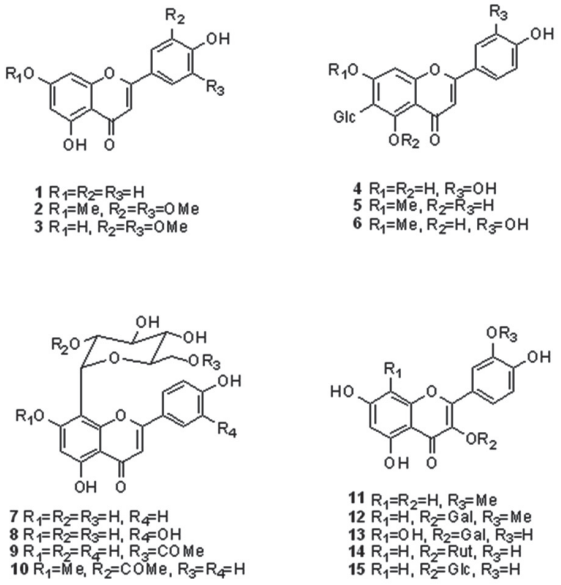
Some members of the *Ouratea* genus have been used in traditional medicine in Brazil and many African countries, including Cameroon, Nigeria, Congo and Gabon (Bouquet, 1969). The leaves and stem are the most commonly used parts of the plant, mainly as the juice form, and as infusions and extracts. In Brazilian traditional medicine, *Ouratea* species have been indicated for the treatment of palsy, erysipelas and uterine wounds (Barroso, 1986). Leaves of *O. spectabilis* are used as stomachic and vermifuge, as well as for the treatment of gastric distress (Braga, 1960). Leaf infusions of *O. parviflora* have long been prescribed for the treatment of inflammation-related diseases such as rheumatism, sprains and arthritic disorders (Carbonari et al., 2006), and further skin diseases (Corrêa, 1975; Paulo et al., 1986; Felício et al., 1995). *O. castaneifolia* is known in the Amazon region of Brazil as "farinha-seca", "mangue-do-mato" or "pau-de-serra" and its bark is used as a tonic and astringent and contains tannins (Le Cointe, 1934). Extracts from the leaves of *O. sulcata*, either alone or in combination with other plants, are used to treat upper respiratory tract infections, dysentery, diarrhoea and toothache (Bouquet, 1969; Pegnyemb et al., 2005). Juices of leaves or flowers of *O. reticulata* are also used as a remedy for toothache. The stems are used internally against dysentery and cough (J.P. Kofani, personal communication; Manga et al., 2001). Extracts of the leaves of *O. elongata*, *O. sulcata* and *O. flava* are used in cases of rheumatic and gastric distress (Gangoué-Piéboji et al. 2006; Mbing et al., 2003a). On the other hand, the compounds responsible for exerting these activities have not been defined, due to a lack of studies on these species.

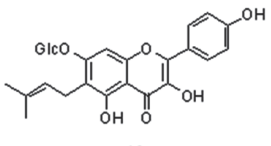
Phytochemistry and chemotaxonomy

Different flavonoids such as flavones (**1-10**), flavonols (**11-16**), flavanonol (**17**), isoflavones (**18-27**), and flavan-3-ol (**28-31**), have been identified in several *Ouratea* species. Only three flavone aglycones were reported in this genus, apigenin (**1**) in *O. parviflora* (Araújo et al., 2011), and two methyl derivatives: 5,4'-dihydroxy-3',5',7-trimethoxyflavone (**2**) (Nascimento et al., 2009), and 5,7,4'-trihydroxy-3',5'-dimethoxyflavone (**3**) (Suzart, 2007b) isolated from the leaves of *O. castaneifolia* and *O. cuspidata*, respectively.

Phytochemical investigations of the leaves and flower extracts of *O. hexasperma*, allowed the isolation of five *C*-glycosylflavones: 6-*C*-glucopyranosyl-luteolin (**4**), from leaves (Daniel et al., 2005), and swertisin (**5**), swertiajaponin (**6**), vitexin (**7**), and orientin (**8**) from inflorescence (Suzart et al., 2012). The vitexin derivative 6"-*O*-acetylvitexin (**9**) was isolated from the leaves of *O. gilgiana* (Njock et al., 2012), and 2''-*O*-acetyl-7-*O*-methyl vitexin (**10**), was obtained from the leaves of *O. turnarea* (Mbing et al., 2009). The phytochemical study of the stem extract from *O. cuspidata* led to the isolation of 3'-*O*-methyl-quercetin (**11**), and its 3-β-*O*-D-galactopyranosyl derivative (**12**) (Suzart, 2007b). The gossypetin-3-*O*-β-galactopyranoside (**13**) and 8-hydroxy-quercetin derivate were obtained from leaves of *O. parviflora* (Felício et al., 2004). Rutin (**14**) (Suzart et al., 2012), quercetin 3-*O*-glucoside (**15**) (Daniel et al., 2005), and two new prenylflavonoids (6-β-β-dimethylallylkaempferol-7-*O*-β-glucoside (**16**), and 6-β-β-dimethylallylaromadendrin-7-*O*-β-glucoside (**17**)) (Carvalho et al., 2008b) were obtained from flowers, leaves and branches of *O. hexasperma*, respectively.

Isoflavones methoxy derivatives have been mainly found in the wood, stems and stem bark, and less frequently in the leaves and roots, of *Ouratea* species. From the stem extract of *O. ferruginea*, four methyl isoflavones derivatives were isolated: 5,4'-dihydroxy-7,5',3'-trimethoxy-isoflavone (**18**), 7,3'-di-*O*-methylorobol (**19**), 5-hydroxy-7,3'4'5'-tetramethoxy-isoflavone (**20**), and piscigenin (**21**) (Fidelis et al., 2012); in contrast, only the 4',5,7-trimethoxyisoflavone (**22**) (Moreira et al., 1994) was isolated from the roots of *O. hexasperma*, lanceolone (**23**), and 4',5-dimethoxy-6,7-methylenedioxyisoflavone (**24**) was isolated from the leaves of *O. turnarea* (Mbing et al., 2009). Two isoflavones, (**24**) and 3'-methoxyirilone (**25**), with a methylenedioxyl-group at *C*-6, *C*-7 of ring A were isolated from the stem bark of *O. flava* (Mbing et al., 2006). Velandia et al. reported the isolation of two new chlorinated isoflavones from the extract of stem and branches of *O. semisserrata*: the 3',6,8-trichloro-4',5-dihydroxy-7-methoxyisoflavone (**26**) and 3',5',6,8-tetrachloro-4',5-dihydroxy-7-methoxyisoflavone (**27**) (Velandia et al., 1998b; 2002). Three flavan-3-ols, epicatechin (**28**) (Daniel et al., 2005; Fidelis et al., 2012), (-)-3,3',5,5',7-pentahydroxy-4'-methoxyepicatechol (**29**), catechin (**30**) (Monache et al., 1967c), and a cianidin (**31**) (Gartlan et al., 1980) were reported in several *Ouratea* species.





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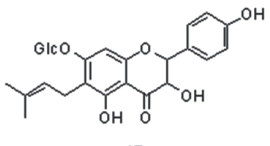

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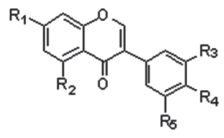
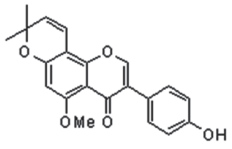


18 R_1=R_3=R_5=OMe, R_2=R_4=OH
19 R_1=R_3=OMe, R_2=R_4=OH, R_5=H
20 R_1=R_3=R_4=R_5=OMe, R_2=OH
21 R_1=R_2=R_4=OH, R_3=R_5=OMe
22 R_1=R_2=R_4=OMe, R_3=R_5=H



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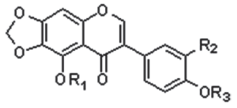
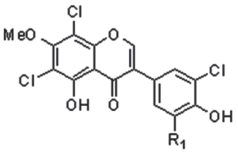
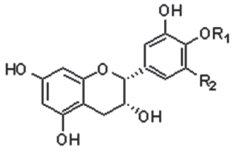


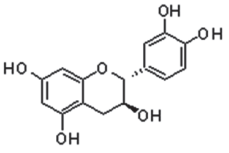
24 R_1=R_3=Me R_2=H
25 R_1=R_3=H, R_2=OMe



26 R_1=H
27 R_1=Cl



28 R_1=R_2=H
29 R_1=Me, R_2=OH



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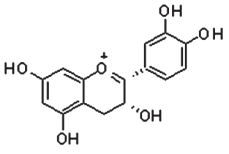
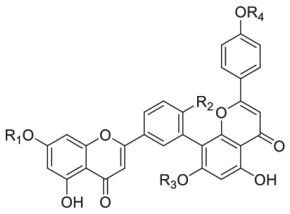
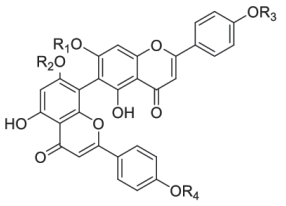


31

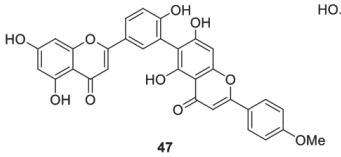
The biflavonoids found in this genus are dimeric compounds of flavone-flavone (**32-53**); flavone-*flava*none (**54-56**); flavone-flavanonol (**57**); flavanonol-flavanonol (**58-59**); chalcone-chalcone (**63-68**); chalcone-flavone (**66**); and, rarely, biisoflavanones (**60-62**), as well as flavan-3-ol dimers (**70-72**) (see Chart 1). Biflavonoids from *Ouratea* genus can be used as chemical markers because they can be used to determine differences among these taxa according to the linkage between the flavonoid units. The biflavones, amentoflavone (**32**, *C*-3'→*C*-8"), agathisflavone (**42**, *C*-6→*C*-8"), and its methyl ether derivatives (**33-46**), were reported mainly in the leaves of several *Ouratea* species. These bioflavonoids are the most indicated as chemotaxonomic markers of this genus. However, other dimers have occasionally been found, such as 4"'-*O*-methyl-robustaflavone (**47**, *C*-3'→*C*-6"), which was reported from the leaves of *O. semisserrata* (Bosso, 2003), and (*C*-6→*C*-6")-bigenkwanin (**48**), isolated together with **45**, from the leaves of *O. spectabilis* (Felício et al., 1995).



32 R_1=R_2=R_3=R_4=H
33 R_1=R_3=R_4=H, R_2=Me
34 R_1=Me, R_2=R_3=R_4=H
35 R_1=R_2=R_3=H, R_4=Me
36 R_1=R_3=Me, R_2=R_4=H
37 R_1=R_2=H, R_3=R_4=Me
38 R_1=R_2=Me, R_3=R_4=H
39 R_1=R_4=Me, R_2=R_3=H
40 R_1=R_3=R_4=Me, R_2=H
41 R_1=R_2=R_3=R_4=Me



42 R_1=R_2=R_3=R_4=H
43 R_1=R_3=R_4=H, R_2=Me
44 R_1=R_2=R_4=H, R_3=Me
45 R_1=R_2=Me, R_3=R_4=H
46 R_1=R_2=H, R_3=R_4=Me



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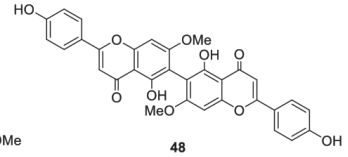

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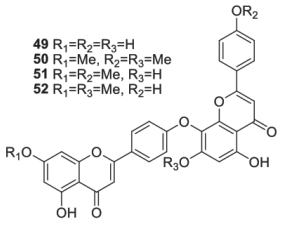
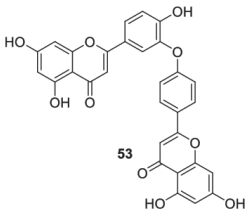


49 R_1=R_2=R_3=H
50 R_1=Me, R_2=R_3=Me
51 R_1=R_2=Me, R_3=H
52 R_1=R_3=Me, R_2=H



53

Biflavonoids containing an oxygen linking the unities such as those known as Ochnaflavone (*C*-3'-O→*C*-4'")(**53**) (Zintchem et al., 2007), lanaraflavone (*C*-4'-O→*C*-8")(**49**) and its two methyl ether (**50-51**), were isolated from the leaves of *O. semisserrata*, and **52** was isolated from the leaves of *O. hexasperma* (Velandia et al., 2002; Daniel et al., 2005). The Ochnaflavone (**53**) is rarely found in *Ouratea*; it was isolated only from *O. staudtii* (Zintchem et al., 2007).

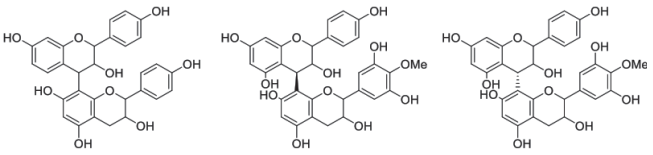
Other dimers (*C*-6→*C*-8") of the flavone-flavanone type: zenkeriane A (**54**), zenkeriane B (**55**), and rhusflavone (**56**) were obtained from the leaves of *O. zenkeri* (Mbing et al., 2009), as well as a new flavanonol dimer, 3-hydroxy-4',5,7-trimethoxyflavone-(*C*-6→*C*-8")-3"-hydroxy-3"',4"',5",7"-tetramethoxyflavone (**59**), which was isolated from the leaves of *O. multiflora* (Felício et al., 2001). Sulcatone A (**57**), a flavone-flavanonol, and 3-hydroxy-2,3-dihydroapigenyl-(*C*-4"'-O→*C*-3')-dihydrokaempferol (**58**), a flavanone-flavanonol, were isolated from leaves of *O. sulcata* (Pegnyemb et al., 2005).

The roots of *O. hexasperma*, collected in the Amazonian cerrado, yielded three biisoflavanones, hexaspermone A (**60**), B (**61**) and C (**62**), which were reported for the first time in the literature (Moreira et al., 1994).

Chalcone dimers are found in several *Ouratea* species, mainly in African species. Lophirone A (**63**) and lophirone G (**64**) were obtained from the leaves from *Ouratea* species (see Chart 1). The occurrence of biflavonoids in the stem bark and root is less frequent, but chalcone dimers of complex structure, including flavumone A (**65**), calodenin B (**66**) and C (**70**), isolated from *O. flava*; lophirone C (**67**) and isolophirone C (**68**), obtained from *O. turnarea*; and the chalcone-flavone dimer, named flavumone B (**66**), also isolated from *O. flava*

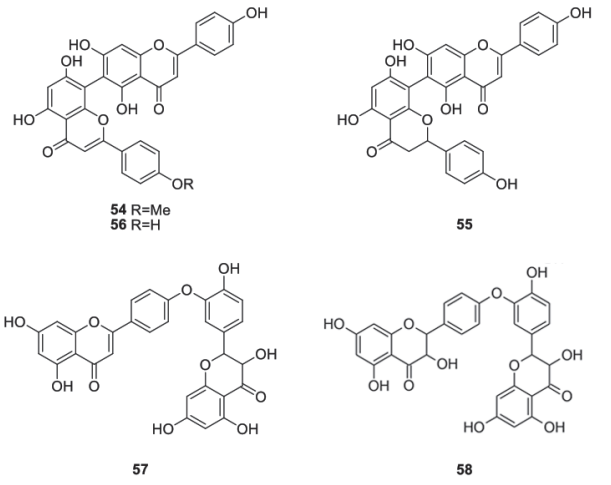
(Mbing et al., 2003a; Zintchem et al., 2008), are rarely found in Brazilian species.

Two epimers, proantocianidin A (**71**) and B (**72**), were isolated from the root of *Ouratea* sp. (Monache et al.,1967a,b; 1970). Compounds **70-72** were the only proantocyanidin dimers obtained from *Ouratea* genus. A flavanol dimer isolated from *Ouratea* sp. showed antitumoral activity against sarcoma-180 and Walker 256 *in vivo* (Oliveira et al., 1972).



70 **71** **72**

The triterpenes are usually present in leaves, branches, flowers and stems of *Ouratea* species, while none were reported from roots (see Chart 2). The triterpenes α-amyrin (**73**), β-amyrin (**74**), lupeol (**75**) and friedelin (**78**) are found more frequently. A new triterpene, lup-15,20(**29**)-dien-3β,28-diol (**83**), besides **75**, was isolated from the ethanol extract of leaves of *O. multiflora* (Felício et al., 2001a). Three diterpenes were isolated in the two *Ouratea* species: 16α-hydroxykaurane (**84**) and 16α-hydroxykaurane-19-oic acid (85) from *O. parviflora* (Felício et al., 2004), and 16α,17-dihydroxykauran-19-oic acid (**86**) from *O. semisserrata* (Velandia et al., 1998a). Sitosterol (**87**), stigmasterol (**88**) and campesterol (**89**) can be recovered as a mixture, and 3-*O*-β-glycopyranosylsitosterol (**90**) and 3-*O*-β-glycopyranosylstigmasterol (**91**) were yielded as a mixture in several species of *Ouratea* genus. Other steroids, such as 7-oxostigmat-5-en-3β-ol (**92**) and 7-oxostigmasta-5,22-dien-3β-ol (**93**), have only been obtained from *O. semisserrata* (Velandia et al., 2002).



54 R=Me
56 R=H

55

57 **58**

59

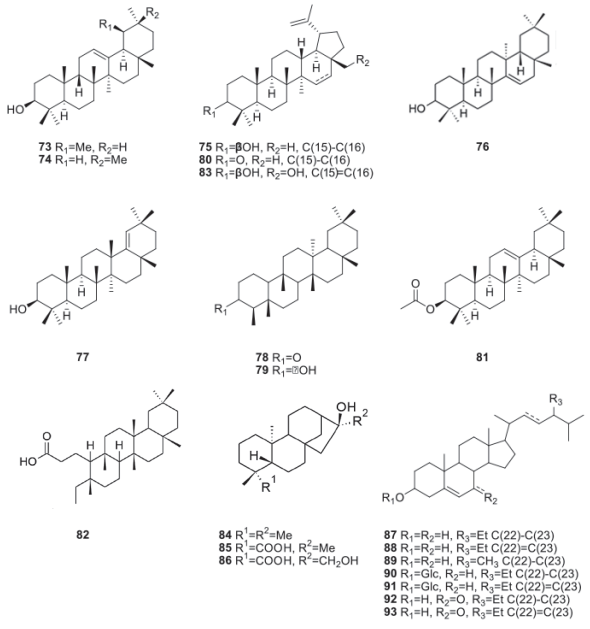
60 R_1=H, R_2=Me
61 R_1=Me, R_2=H
62 R_1=R_2=H

63 **64**

65 R_1=OH
66 R_1=H

67

68 **69**



73 R_1=Me, R_2=H
74 R_1=H, R_2=Me

75 R_1=βOH, R_2=H, C(15)-C(16)
80 R_1=O, R_2=H, C(15)-C(16)
83 R_1=βOH, R_2=OH, C(15)=C(16)

76

77

78 R_1=O
79 R_1=βOH

81

82

84 R^1=R^2=Me
85 R^1=COOH, R^2=Me
86 R^1=COOH, R^2=CH_2OH

87 R_1=R_2=H, R_3=Et C(22)-C(23)
88 R_1=R_2=H, R_3=Et C(22)=C(23)
89 R_1=R_2=H, R_3=CH_3 C(22)-C(23)
90 R_1=Glc, R_2=H, R_3=Et C(22)-C(23)
91 R_1=Glc, R_2=H, R_3=Et C(22)=C(23)
92 R_1=H, R_2=O, R_3=Et C(22)-C(23)
93 R_1=H, R_2=O, R_3=Et C(22)=C(23)

Several other constituents were isolated from *Ouratea* species. Some of these compounds such as lignin (**94-95**), norisoprenoid (**96**), dihydrobenzofuranones (**105-106**), depside (**107**), and indole alkaloid (**108**), as well as carbohydrates, benzoic and cinnamic acid derivates and a mixture of fat acid esters have been found less frequently in this genus (Estevam et al., 2006; Rosa, 1939a,b). Chart 3 shows constituents **94-137.**

Chart 1.
Flavonoids (**1-31**) and biflavonoids (**32-72**) from *Ouratea* species.

No.	Compounds	Plant	Part	Reference
1	apigenin	*O. parviflora*	Leaves	Araújo et al., 2011
2	5,4'-dihydroxy-3',5',7-trimethoxyflavone	*O. castaneifolia*	Stem	Nascimento et al., 2009
3	5,74'-trihydroxy-3',5'-dimethoxyflavone	*O. cuspidata*	Leaves	Suzart, 2007b
4	6-C-glucopyranosyl-luteolin	*O. hexasperma*	Leaves	Daniel et al, 2005
5	swertisin	*O. hexasperma*	Flower	Suzart et al., 2012
6	swertiajaponin	*O. hexasperma*	Flower	Suzart et al., 2012
7	vitexin	*O. hexasperma*	Flower	Suzart et al., 2012
8	orientin	*O. hexasperma*	Flower	Suzart et al., 2012
9	6"-O-acetylvitexin	*O. gilgiana*	Leaves	Njock et al., 2012
10	2"-O-acetyl-7-O-methylvitexin	*O. turnarea*	Leaves	Mbing et al., 2009
11	3'-O-methyl-quercetin	*O. cuspidata*	Stem	Suzart, 2007b
12	5,7,4'-trihydroxy-3'-methoxy-3-β-O-D-galactopyranosylflavone	*O. cuspidata*	Stem	Suzart, 2007b
13	gossypetin-3-O-β-galactopyranoside	*O. parviflora*	Leaves	Felicio et al., 2004
14	rutin	*O. hexasperma*	Flower	Suzart et al., 2012
15	quercetin-3-O-glucoside	*O. hexasperma*	Leaves	Daniel et al, 2005
16	6-β-β-dimethylallylkaempferol-7-O-β-glucoside	*O. hexasperma*	Branches	Carvalho et al., 2008b
17	6-β-β-dimethylallylaromadendrin-7-O-β-glucoside	*O. hexasperma*	Branches	Carvalho et al., 2008b
18	5,4'-dihydroxy-7,5',3'-trimethoxy-isoflavone	*O. ferruginea*	Stem	Fidelis et al., 2012
19	7,3'-di-O-methylorobol	*O. ferruginea*	Stem	Fidelis et al., 2012
20	5-hydroxy-7,3'4'5'-tetramethoxy-isoflavone	*O. ferruginea*	Stem	Fidelis et al., 2012
21	piscigenin	*O. ferruginea*	Stem	Fidelis et al., 2012
22	4',5,7-trimethoxyisoflavone	*O. hexasperma*	Root	Moreira et al., 1994
23	lanceolone	*O. turnarea*	Leaves	Mbing et al., 2009
24	4',5-dimethoxy-6,7-methylenedioxyisoflavone	*O. turnarea*	Leaves	Mbing et al., 2009
		O. flava	Stem bark	Mbing et al., 2006
25	3'-methoxyirilone	*O. flava*	Stem bark	Mbing et al., 2006
26	3',6,8-trichloro-4',5-dihydroxy-7-methoxyisoflavone	*O. semisserrata*	Wood	Velandia et al., 1998b
		O. semisserrata	Branches	Velandia et al., 2002
27	3',5',6,8-tetrachloro--4',5-dihydroxy-7-methoxyisoflavone	*O. semisserrata*	Wood	Velandia et al., 1998b
		O. semisserrata	Branches	Velandia et al., 2002

(cont.)

Chart 1. *cont.*

28	epicatechin	*O. ferruginea*	Leaves	Fidelis et al., 2012
		O. hexasperma	Leaves	Daniel et al., 2005
29	(-)-3,3',5,5',7-pentahydroxy-4'-methoxyepicatechol	*O. sp.*	Root	Monache et al., 1967
30	catechin	*O. sp.*	Root	Monache et al., 1967
31	cianidin	*O. affins*	-	Gartlan et al., 1980
		O. calantha	-	Gartlan et al., 1980
32	amentoflavone	*O. aquatica*	Leaves	Lima et al., 2006
		O. castaneifolia	Leaves	Nascimento et al., 2009
		O. cuspidata	Leaves	Suzart et al;., 2007b
		O. elongata	Leaves	Bikobo et al., 2009
		O. ferruginea	Leaves	Fidelis et al., 2012
		O. gilgiana	Leaves	Njock et al., 2012
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. multiflora	Leaves	Felício et al., 2001a
		O. parviflora	Leaves	Araújo et al., 2011
		O. semisserrata	Leaves	Velandia et al., 2002
		O. staudtii	Leaves	Zintchem et al., 2007
		O. sulcata	Leaves	Pegnyemb et al., 2005
		O. turnarea	Root	Zintchem et al., 2008
		O. zenkeri	Leaves	Mbing et al., 2009
33	bilobentin	*O. elongata*	Leaves	Bikobo et al., 2009
		O. staudtii	Leaves	Zintchem et al., 2007
34	sequoieflavone	*O. ferruginea*	Leaves	Fidelis et al., 2012
		O. elongata	Leaves	Bikobo et al., 2009
35	podocarpusflavone A	*O. elongata*	Leaves	Bikobo et al., 2009
		O. multiflora	Leaves	Carbonezi et al., 2007
		O. semisserrata	Leaves	Velandia et al., 2002
		O. semisserrata	Branches	Velandia et al., 2002
		O. staudtii	Leaves	Zintchem et al., 2007
36	7,7”-di-*O*-methylamenthoflavone	*O. castaneifolia*	Leaves	Nascimento et al., 2009
37	7”,4’”-di-*O*-methylamenthoflavone-	*O. multiflora*	Leaves	Carbonezi et al., 2007
38	7,4’-di-*O*-metilamentoflavone	*O. semisserrata*	Leaves	Bosso, 2003
39	putraflavone	*O. cuspidata*	Leaves	Suzart, 2007b
40	heveaflavone	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. multiflora	Leaves	Carbonezi et al., 2007
41	4’,4”’,7,7”-tetra-*O*-methylamenthoflavone	*O. castaneifolia*	Leaves	Nascimento et al., 2009
42	agathisflavone	*O. gilgiana*	Leaves	Njock et al., 2012

(cont.)

Chart 1. *cont.*

		O. hexasperma	Leaves	Daniel et al., 2005
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. nigroviolacea	Leaves	Mbing et al., 2006
		O. parviflora	Leaves	Araújo et al., 2011
		O. staudtii	Leaves	Zintchem et al., 2007
		O. sulcata	Leaves	Pegnyemb et al., 2005
43	7”-*O*-methylagathisflavone	*O. hexasperma*	Leaves	Daniel et al., 2005
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. parviflora	Leaves	Araújo et al., 2011
44	ouratine B	*O. nigroviolacea*	Leaves	Mbing et al., 2006
45	7,7”-di-*O*-methylagathisflavone	*O. spectabilis*	Leaves	Felício et al., 1995
		O. parviflora	Leaves	Felício et al., 2004
46	ouratine A	*O. nigroviolacea*	Leaves	Mbing et al., 2006
47	4’’’-*O*-methylrobustaflavone	*O. semisserrata*	Leaves	Bosso, 2003
48	(6→6”)-bigenkwanin	*O. spectabilis*	Leaves	Felício et al., 1995
49	lanaraflavone	*O. semisserrata*	Leaves	Velandia et al., 2002
50	7-*O*-methyllanaraflavone	*O. semisserrata*	Leaves	Velandia et al., 2002
51	7,4’”-di-*O*-methyllanaraflavone	*O. semisserrata*	Leaves	Velandia et al., 2002
52	7,7”-di-*O*-methyllanaraflavone	*O. hexasperma*	Leaves	Daniel et al., 2005
53	ochnaflavone	*O. staudtii*	Leaves	Zintchem et al., 2007
54	zenkeriane A	*O. zenkeri*	Leaves	Mbing et al., 2009
55	zenkeriane B	*O. zenkeri*	Leaves	Mbing et al., 2009
56	rhusflavone	*O. zenkeri*	Leaves	Mbing et al., 2009
57	sulcatone A	*O. sulcata*	Leaves	Pegnyemb et al., 2005
58	3-hydroxy-2,3-dihydroapigenyl-(C-4’-O→C-3’)-dihydrokaempferol	*O. sulcata*	Leaves	Pegnyemb et al., 2005
59	3-hydroxy-4’,5,7-trimethoxyflavone-(C-6-O→C-8”)-3”-hydroxy-3”’,4”’,5”,7”-tetramethoxyflavone	*O. multiflora*	Leaves	Carbonezi et al., 2007
60	hexasperma A	*O. hexasperma*	Root	Moreira et al., 1994
61	hexasperma B	*O. hexasperma*	Root	Moreira et al., 1994
62	hexasperma C	*O. hexasperma*	Root	Moreira et al., 1994
63	lophirone A	*O. elongata*	Leaves	Bikobo et al., 2009
		O. flava	Leaves	Mbing et al., 2003b
		O. flava	Stem bark	Mbing et al., 2003a
		O. staudtii	Leaves	Zintchem et al., 2007
		O. sulcata	Leaves	Pegnyemb et al., 2005
		O. turnarea	Leaves	Mbing et al., 2009
		O. zenkeri	Leaves	Mbing et al., 2009

(cont.)

Chart 1. *cont.*

64	lophirone G	*O. flava*	Leaves	Mbing et al., 2003b
65	flavumone A	*O. flava*	Stem bark	Mbing et al., 2003a
66	calodenin B	*O. flava*	Stem bark	Mbing et al., 2003a
		O. turnarea	Root	Zintchem et al., 2008
67	lophirone C	*O. turnarea*	Root	Zintchem et al., 2008
68	isolophirone C	*O. turnarea*	Root	Zintchem et al., 2008
69	flavumone B	*O. flava*	Stem bark	Mbing et al., 2003a
70	calodenin C	*O. flava*	Stem bark	Mbing et al., 2003a
71	proantocianidin A	*O. sp.*	Root	Oliveira et al., 1972
72	proantocianidin B	*O. sp.*	Root	Oliveira et al., 1972

Chart 2.
Terpenoids (**73-86**) and steroids (**87-93**) from *Ouratea* species

No.	Compounds	Plant	Part	Reference
73	α-amirin	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. cuspidata	Leaves	Suzart et al., 2007a
		O. microdonta	Leaves	Carvalho et al., 2008a
74	β-amirin	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. cuspidata	Leaves	Suzart et al., 2007a
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. nitida	Leaves	Estevam et al., 2006
75	lupeol	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. cuspidata	Leaves	Suzart et al., 2007a
		O. flava	Leaves	Mbing et al., 2003b
		O. floribunda	Wood	Carvalho et al., 2000
		O. hexasperma	Branches	Carvalho et al., 2008b
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. semiserrata	Leaves	Velandia et al., 2002
76	taraxerol	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. castaneifolia	Stem	Nascimento et al., 2009
77	germanicol	*O. castaneifolia*	Leaves	Nascimento et al., 2009
78	friedelin	*O. castaneifolia*	Stem	Nascimento et al., 2009
		O. ferruginea	Leaves	Fidelis et al., 2012
		O. floribunda	Wood	Carvalho et al., 2000
		O. nitida	Leaves	Estevam et al., 2006
		O. parviflora	Leaves	Araújo et al., 2012
		O. semiserrata	Leaves	Velandia et al., 2002
79	3-β-friedelinol	*O. castaneifolia*	Stem	Nascimento et al., 2009
		O. ferruginea	Leaves	Fidelis et al., 2012

(cont.)

Chart 2. *cont.*

		O. floribunda	Wood	Carvalho et al., 2000
80	lupeone	*O. ferruginea*	Leaves	Fidelis et al., 2012
		O. flava	Leaves	Mbing et al., 2003b
81	3-β-O-acyl-olean-12-en-28-oic acid	*O. hexasperma*	Flower	Suzart et al., 2012
82	3,4-*seco*-friedelan-3-oic acid	*O. nitida*	Leaves	Estevam et al., 2006
83	lup-15,20(29)-dien-3β,28-diol	*O. multiflora*	Leaves	Felício et al., 2001b
84	16α-hydroxykaurane	*O. parviflora*	Leaves	Felício et al., 2004
85	16α-hydroxykaurane-19-oic	*O. parviflora*	Leaves	Felício et al., 2004
86	16α,17-dihydroxykauran-19-oic acid	*O. semiserrata*	Leaves	Velandia et al., 1998a
87	sitosterol	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. ferruginea	Leaves	Fidelis et al., 2012
		O. hexasperma	Branches	Carvalho et al., 2008b
		O. hexasperma	Flower	Suzart et al., 2012
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. parviflora	Leaves	Araújo et al., 2012
		O. semiserrata	Leaves	Velandia et al., 2002
		O. semiserrata	Branches	Velandia et al., 2002
88	stigmasterol	*O. castaneifolia*	Leaves	Nascimento et al., 2009
		O. ferruginea	Leaves	Fidelis et al., 2012
		O. hexasperma	Branches	Carvalho et al., 2008b
		O. hexasperma	Flower	Suzart et al., 2012
		O. microdonta	Leaves	Carvalho et al., 2008a
		O. nigroviolacea	Leaves	Mbing et al., 2006
		O. parviflora	Leaves	Felício et al., 2004
		O. semiserrata	Leaves	Velandia et al., 2002
		O. semiserrata	Branches	Velandia et al., 2002
		O. sulcata	Leaves	Pegnyemb et al., 2005
89	campesterol	*O. ferruginea*	Leaves	Fidelis et al., 2012
		O. hexasperma	Branches	Carvalho et al., 2008b
		O. parviflora	Leaves	Araújo et al., 2012
90	3-O-β-glycopyranosylsitosterol	*O. ferruginea*	Leaves	Fidelis et al., 2012
		O. gilgiana	Leave	Njock et al., 2012
		O. hexasperma	Branches	Carvalho et al., 2008b
		O. hexasperma	Flower	Suzart et al., 2012
91	3-O-β-glycopyranosylstigmasterol	*O. ferruginea*	Leaves	Fidelis et al., 2012
		O. sulcata	Leaves	Pegnyemb et al., 2005

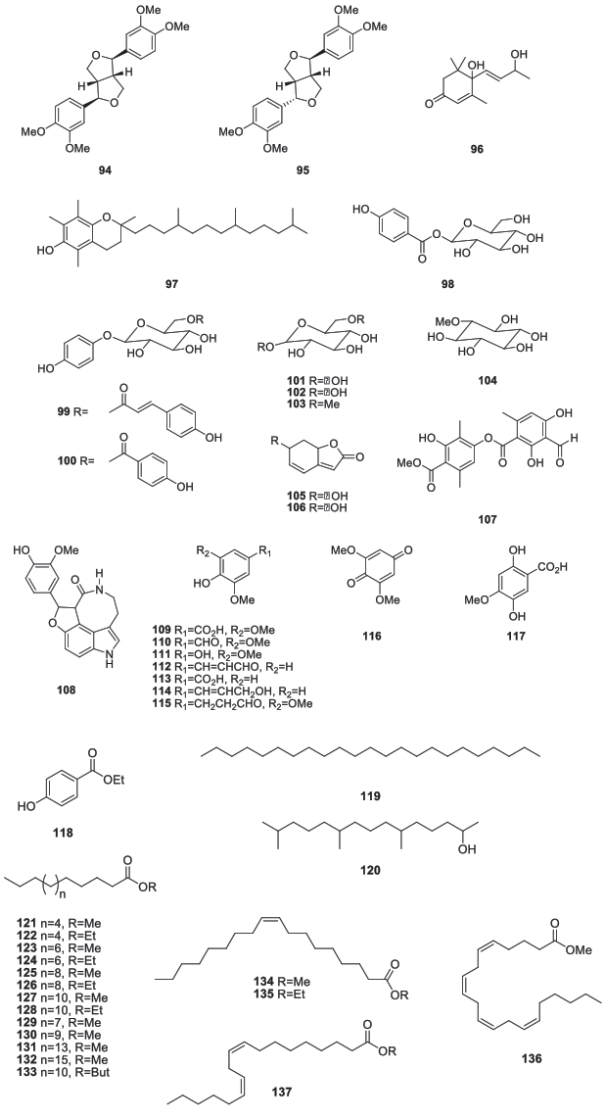
Chart 3.
Others compounds (**94-137**) from *Ouratea* species

No.	Compounds	Plant	Part	Reference
92	7-oxostigmat-5-en-3β-ol	*O. semiserrata*	Branches	Velandia et al., 2002
93	7-oxostigmata-5,22-dien-3β-ol	*O. semiserrata*	Branches	Velandia et al., 2002
94	eudesmin	*O. semisserrata*	Branches	Velandia et al., 2002
95	epieudesmin	*O. semisserrata*	Branches	Velandia et al., 2002
96	6,9-dihydroxymegastigma-4,7-dien-3-one	*O. parviflora*	Leaves	Araújo et al., 2012
		O. semisserrata	Leaves	Velandia et al., 2002
97	tocopherol	*O. parviflora*	Leaves	Araújo et al., 2012
		O. semisserrata	Leaves	Velandia et al., 2002
98	1β-*O*-(4-hydroxybenzoyl)-β-D-glucopyranoside	*O. semisserrata*	Leaves	Velandia et al., 2002
99	1β-*O*-(4-hydroxyphenyl)-6-*O*-(4-methoxycinamoyl)-D-glucopyranoside	*O. semisserrata*	Leaves	Velandia et al., 2002
100	1β-*O*-(4-hydroxyphenyl)-6-*O*-(4-hydroxybenzoyl)-D-glucopyranoside	*O. parviflora*	Leaves	Felício et al., 2004
		O. semisserrata	Leaves	Velandia et al., 2002
101	α-D-glucopyranose	*O. semisserrata*	Leaves	Velandia et al., 2002
102	β-D-glucopyranose	*O. semisserrata*	Leaves	Velandia et al., 2002
103	methyl-β-D-glycopyranoside	*O. cuspidata*	Stem	Suzart et al., 2007a
104	methyl myoinositol	*O. hexasperma*	Leaves	Moreira et al., 1999
105	aquilegiolide	*O. reticulata*	Root bark	Manga et al., 2001
106	menisdaurilide	*O. reticulata*	Root bark	Manga et al., 2001
107	atranorin	*O. floribunda*	Wood	Carvalho et al., 2000
108	serotobenine	*O. gilgiana*	Leaves	Njock et al., 2012
		O. turnarea	Root	Zintchem et al., 2008
109	syringic acid	*O. gilgiana*	Leaves	Njock et al., 2012
		O. ferruginea	Leaves	Fidelis et al., 2012
110	syringic aldehyde	*O. ferruginea*	Stem	Fidelis et al., 2012
111	2,6-dimethoxyhydroquinone	*O. ferruginea*	Stem	Fidelis et al., 2012
112	ferulic aldehyde	*O. ferruginea*	Stem	Fidelis et al., 2012
113	vanillic acid	*O. ferruginea*	Stem	Fidelis et al., 2012
114	1-hydroxy-2-methoxy-4-(1E-3-hydroxy-1-propenyl)-benzene	*O. ferruginea*	Stem	Fidelis et al., 2012
115	3,5-dimethoxy-4-hydroxydihydrocinamaldehyde	*O. ferruginea*	Stem	Fidelis et al., 2012
116	2,6-dimethoxybenzoquinone	*O. ferruginea*	Stem	Fidelis et al., 2012
117	4-methoxy-2,5-dihydroxy-benzoic acid	*O. microdonta*	Leaves	Carvalho et al., 2008a
118	*p*-hydroxybenzoic acid ethyl ester	*O. nitida*	Leaves	Estevam et al., 2006
119	detracosan	*O. nitida*	Leaves	Estevam et al., 2006
120	6,10,14-trimethyl-2-pentadecanone	*O. nitida*	Leaves	Estevam et al., 2006
121	methyl ester of lauric acid	*O. nitida*	Leaves	Estevam et al., 2006

(cont.)

Chart 3. *cont.*

122	ethyl ester of lauric acid	*O. nitida*	Leaves	Estevam et al., 2006
123	methyl ester of myristic acid	*O. nitida*	Leaves	Estevam et al., 2006
124	ethyl Ester of myristic acid	*O. nitida*	Leaves	Estevam et al., 2006
125	methyl ester of palmitic acid	*O. nitida*	Leaves	Estevam et al., 2006
126	ethyl ester of palmitic acid	*O. nitida*	Leaves	Estevam et al., 2006
127	methyl ester of stearic acid	*O. nitida*	Leaves	Estevam et al., 2006
128	ethyl ester of stearic acid	*O. nitida*	Leaves	Estevam et al., 2006
129	methyl ester of pentadecanoic			
130	methyl ester of heptadecanoic			
131	methyl ester of beenic			
132	methyl ester of lignoceric			
133	*n*-butyl stearate			
134	methyl ester of oleic acid	*O. nitida*	Leaves	Estevam et al., 2006
135	ethyl ester of oleic acid	*O. nitida*	Leaves	Estevam et al., 2006
136	methyl ester of arachidonic	*O. nitida*	Leaves	Estevam et al., 2006
137	ethyl ester of linoleic acid	*O. nitida*	Leaves	Estevam et al., 2006



Biological activities

The crude extracts as well as pure compounds obtained from *Ouratea* species possess a number of biological activities that have been reported from time to time.

Antiviral activity

Viral infections remain a major threat to humans and animals and there is a crucial need for new antiviral agents, especially with the development of resistant viruses (Bagla et al., 2012). Extracts from the leaves from *Ouratea lucens* were evaluated for antiviral activity as well as for their cytotoxic effects against herpes virus 1 (HSV-1) and (HSV-2) 2, poliovirus, vesicular stomatitis virus (VSV), and parainfluenza-3 virus. Good antiviral activities of ethanol and aqueous extracts were observed against HSV-1 and HSV-2, while petroleum ether extract showed similar activities only on HSV-1, as determined by a VR assay. The dichloromethane extract showed slight activities against HSV-1 and HSV-2. Similar results were observed in the DPI assay. The ethanol extract displayed a higher activity against VSV, as the aqueous extract was more active against HSV-1, both with an ED_{50} at 9 µg/ml. For Para 3 virus infections, aqueous extracts were most active, with an ED_{50} at 20 µg/ml, while ethanol extract had the best activity against Polio-1 with an ED_{50} at 30 µg/ml. The used concentrations of extracts do not have cytotoxic effects (Roming et al., 1992).

The ethanol extracts of *Ouratea castaneifolia*, *O. semiserrata* and *O. spectabilis* displayed activity against human herpes virus type 1 (HSV-1), vaccinia virus (VACV) and murine encephalomyocarditis virus (EMCV), assayed by MTT, against positive controls (acyclovir/Calbiochem and α-2a interferon/Bergamo). Leaves extracts from *Ouratea spectabilis* showed activity against HSV-1, with EC_{50} values lower than 50 µg/ml, while leaves extracts from *O. castaneifolia* and *O. semiserrata* were moderately active, with EC_{50} values ranging from 56.5

to 97.24 µg/ml, respectively. Moderate to low activity against EMCV, was observed for extracts from *Ouratea* castaneaefolia (EC_{50} 185.9 µg/ml) and *O. semiserrata* (EC_{50} 465.7 µg/ml). The extracts from *Ouratea spectabilis*, *O. castaneifolia* and *O. semiserrata* inhibited the replication of VACV-WR, a DNA-virus, with EC_{50} values below 50 µg/ml. Among the active extracts, the one from *O. semiserrata* should be highlighted due to the EC_{50} at 7.4 µg/ml (Brandão et al., 2011).

Agathisflavone (**42**), 7"-methyl-agathisflavone (**43**) and lupeol (**75**), obtained from *O. parviflora*, were assayed for antiviral activities against HSV-1 with 50% ED (ED_{50}) values of 11.2, 25.8 and 47.5 µg/ml, respectively. Regarding anti-HSV-2 activity, **42** and **43** presented ED_{50} values of 2.8 and 1.5, respectively, whereas **75** did not show anti-HSV-2 activity (Araújo et al., 2011).

Anti-tumour and anticancer activity

Cancer is responsible for high rates of human mortality. Many chemotherapeutics currently used in cancer therapy are tumour growth inhibiting agents that hinder DNA replication and transcription (Sharma, 2013).

A flavanol dimer isolated from *Ouratea* sp., was assayed for anti-tumour activity against Sarcoma 180 in mice and Walker 256 in rats. The proantocianidin (**71-72**), whose absolute configuration was not mentioned by the authors, showed significant anti-tumour activity. Doses of 300 mg/kg/day, *i.p.* for five days decreased tumour growth by 50-70% (Oliveira et al., 1972).

The cytotoxic and anti-tumour activities against murine tumours were evaluated *in vivo* for **43**, **32**, and **32a**, by MTT assays. 7''-*O*-methyl-agathisflavone (**43**) induced significant growth delay against Sarcoma 180 (S180) cells, with IC_{50} values of DNA and protein synthesis at 3 and 6.8 µM, respectively, as well as anti-tumour activity against an ascitic S180 tumour at a dose of 80 mg/kg (% T/C 140), in which 5-fluorouracil, used as a positive control, at a dose of 38 mg/kg (% T/C 140) showed equal values (Grynberg et al., 1994).

DNA topoisomerases are a class of enzymes involved in the regulation of DNA supercoiling, crucial for the replication and transcription of DNA. Consequently, these enzymes are targets for chemotherapeutic intervention in antibacterial and anticancer therapies (Ishar et al., 2006). In 2002, Grynberg et al. reported the effect of the biflavonoids 7''-*O*-methyl-agathisflavone (**43**), isolated from *Ouratea hexasperma*, amentoflavone (**32**) obtained from *O. semiserrata*, and the acetyl derivative of 32 (**32a**) on Ehrlich ascitic carcinoma cells, human K562 leukemic cell line and action on the human DNA topoisomerases I and II-α. All compounds were shown to be inhibitors of human DNA topoisomerases I at 200 µM, and only 7''-*O*-methyl-agathisflavone (**43**) at 200 µM inhibited DNA topoisomerases II-α. The biflavonoids showed concentration-dependent growth inhibitory activities on Ehrlich carcinoma cells in a 45-h culture, assayed by a tetrazolium method, with IC_{50} 24 µM for I, 26 µM for II and 10 µM for IIα. These biflavonoids were assayed on human K562 cell line in 45-h culture, but only 7''-*O*-methyl-agathisflavone (**43**) showed 42% growth inhibitory activity at 90 µM. Posteriorly, cytotoxic and anti-tumour activities against murine tumours were evaluated *in vivo* for **43**, **32**, and **32a**, by the MTT assays. 7''-*O*-methyl-agathisflavone (**43**) showed significant growth delay against Sarcoma 180 (S180) cells, with IC_{50} values of DNA and protein synthesis at 3 and 6.8 µM, resp., as well as anti tumour activity against an ascitic S180 tumour at a dose of 80 mg/kg (% T/C 140), in which 5-fluorouracil, used as a positive control, at a dose of 38 mg/kg (% T/C 140) showed equal values.

Biflavonoids 7,7''-dimethyllanaraflavone (**52**), agathisflavone (**42**) and 7''-methylagathisflavone (**43**) isolated from the leaves of *O. hexasperma*, as well as a mixture of **52** and **43**, were assayed against HT-29 colon adenocarcinoma, NCI-H460 non-small cell lung carcinoma, MCF-7 breast cancer cell, OVCAR-3 ovarian adenocarcinoma cells, and RXF-393 renal cell carcinoma, using etoposide as a reference compound. Compound **52** promoted growth inhibitory activity at 3-5 µg/ml (< 25% control growth) in NCI-H460, MCF-7, and OVCAR-3 cell lines; this effect was also confirmed by the low values of IC_{50} for these cell lines (0.77-2.5 µg/ml). However, for HT-29 and RXF-393 cell lines, this compound induced a comparatively low cytotoxic effect. Compound **43** showed the highest activity, with an IC_{50} value of around 4 µg/ml for all five of the cell lines tested. A mixture of **52** and **43** showed growth inhibition activity (< 25% of control cell growth) among the cell lines tested at 18-20 µg/ml, with IC_{50} values ranging from 8-10 µg/ml. Compound **42** did not have any significant effect on cell growth in any of the cell lines tested (Daniel et al., 2007).

Biflavonoids heveaflavone (**40**), 7'',4'''-di-*O*-methylamentoflavone (**37**), podocarpusflavone-A (35), and amentoflavone (**32**), obtained from leaves of *Ouratea multiflora*, were assayed for cytotoxicity toward mouse lymphoma (L5178) and a melanoma cancer cell line (KB). None of the compounds were active against this cell line (Carbonezi et al. 2007).

Anti-inflammatory activity

Reactive oxygen species (ROS) are intimately involved in the pathogenesis of inflammatory processes and they can exacerbate tissue damage. In addition to the protective effects of the endogenous antioxidant defence system, natural products with antioxidant activity are also important to attenuate oxidative damage, complementing those defences (Carbonari et al., 2006). The antioxidant potential of crude extracts (CEOP) and fractions (OP4) from leaves of *O. parviflora* revealed anti-inflammatory effects *in vitro* through the scavenging of radicals 2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH), hydroxyl radical ($HO^{\bullet}$, by deoxyribose method), superoxide anion ($O2^{\bullet-}$, according to Robak & Gryglewski, 2002), and lipid peroxidation (by TBA method) in rat liver homogenate. The CEOP and OP4 showed strong inhibitory activity to lipid peroxidation induced by tert-butyl peroxide (IC_{50} 2.3 and 1.9 mg/ml, respectively), and concentration-dependent inhibition of deoxyribose oxidation (14.9 and 0.2 µg/ml, respectively), as well as considerable antioxidant activity against $O2^{\bullet-}$ (87.3 and 73.1 µg/ml, respectively) and DPPH radicals (55.4 and 38.3 µg/ml, respectively) (Carbonari et al., 2006).

Lipoxygenases constitute a family of non-haem iron containing dioxygenases widely distributed in animals and plants. It has been found that these lipoxygenase products play

a vital role in a variety of disorders such as bronchial asthma, inflammation and tumour angiogenesis (Zargar et al., 2013). The leaves and stem extracts from *O. semisserrata* showed 29.2 and 7.8% 5-lipoxygenase inhibition, respectively. The *in vitro* assay of inhibition of 5-lipoxygenase constitutes a good model for the screening of plants with antiasthma activity (Braga et al. 2000).

Hepatoprotective activity on carbon tetrachloride-induced hepatoctye injury

Carbon tetrachloride (CCl_4) attacks hepatocytes, causing damage to plasma membranes by lipid peroxidation. The cytosolic enzymes in the injured hepatocytes leak through the cell due to cell permeability. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes are involved in the hepatoprotective activity. The crude extract (CEOP) and hydro-alcoholic fraction (OP4) of *O. parviflora* were considered to be responsible of the hepatoprotective activity on CCl_4-induced damage in rat hepatocytes. The pre-treatment with CEOP and OP4 (300 mg/kg, for seven days) prevented lipid peroxidation, DNA damage and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) release without affecting hepatic GSH content in CCl_4-treated animals (Carbonari et al., 2006). CCl_4 significantly increased (by 90%) levels of lipid hydroperoxides, carbonyl protein content (64%), DNA damage index (133%), AST (261%), ALT (212%), and catalase activity (23%), and also caused a decrease of 60% in GSH content (Carbonari et al., 2006).

Enzyme inhibition activity

For a long time, the biological activities of plant polyphenols over plants, as well as in humans, have arguably been attributed to their capacity to exert antioxidant actions and/or to their propensity to form precipitating complexes with proteins in a rather nonspecific manner (Haslam, 1996; Quideau et al., 2011). Today, there is compelling evidence that strongly suggests that the mechanisms by which plant polyphenols exert their protective actions against cardiovascular and neurodegenerative diseases, as well as cancer and diabetes, are not simply due to their redox properties, but rather to their ability to directly bind to target proteins (or peptides) (Quideau et al., 2011).

Aldose reductase is responsible by catalysing the reduction of glucose to sorbitol in the polyol pathway. Excess sorbitol has been linked to a number of ocular diabetic complications including keratopathy, cataract, and retinopathy (Kador, 1988; Sugiyama et al. 2000). Administration of aldose reductase inhibitors at the onset of diabetes or galactosaemia has been shown to prevent these complications (Sugiyama et al. 2000). 7,7"-di-*O*-methylagathisflavone (**45**) and 6,6"-bigenkwanin (**48**), isolated from the EtOH extract of *O. spectabilis*, exhibited inhibitory activities against aldose reductase. The compounds concentrations studied required to produce 50% inhibition of the enzyme-catalysed reaction (**45**, IC_{50} 27.7 µM and 48, IC_{50} 11.9 µM) were good in comparison with quercetin (IC_{50} 31.4 µM), which was used as a control (Felício et al., 1995). The inhibitory activity against bovine lens aldose reductase shown by 45 and 48 represents a potential therapeutic interest in diabetes pathology. Posteriorly, the cytotoxicity of **48**, **45** and **48a** (derivative obtained by methylation of compound 48) was evaluated in SIRC cell line by spectrophotometric measurement. The **48**, **45** and **48a** presented IC_{50} of 381.9 ± 22.29; 426.74 ± 22.05 and 359.7 ± 24.25 mg/ml respectively. These compounds present significant inhibitory activity for aldose reductase of SIRC cell (Simoni et al., 2002).

Inhibition of acetylcholinesterase by drugs raises the levels of acetylcholine and, thus, offers a symptomatic treatment for Alzheimer's disease (Darvesh et al., 2013). Compounds heveaflavone (**40**), 7'',4'''-di-*O*-methylamentoflavone (**37**), podocarpusflavone-A (**35**), and amentoflavone (**32**) were submitted to preliminary TLC screening to select potential acetylcholinesterase inhibitors, in which none inhibited the enzyme at concentrations of 0.1 and 1.0 µM (Carbonezi et al., 2007).

Xenobiotic metabolism (phase I and II) enzymes are widely known for their role in the metabolism of drugs and other foreign compounds. The reactive metabolites may undergo additional metabolism by phase I or II enzymes to inactive products. Therefore, the induction of either phase I or II enzymes can result in an increased detoxification of carcinogens (Moon et al., 2006). The effect of *Ouratea ferruginea*, flavonoids **18**, **19**, **21** and **34**, toward *in vitro* GST (phase II enzyme) and ECOD (phase I enzyme) activity was evaluated. Piscigenin (**21**) and 5,4'-dihydroxy-7,3',5'-trimethoxyisoflavone (**18**) showed the best inhibitory effects, inhibiting almost 70% and 75% of GST activity, respectively. The inhibitory effect of 7,3'-di-*O*-methylorobol (**19**) on GST activity was not observed. GSTs are promising therapeutic targets because specific isozymes are overexpressed in a wide variety of tumours. The study also revealed that the compounds inhibited ECOD activity *in vitro*. Sequoiaflavone (**34**) was the most potent inhibitor, inhibiting ECOD assay by 75.2% in comparison to the control. Isoflavones **18**, **19** and **21** inhibited ECOD activity by 33.1, 22.2 and 56.5%, respectively (Fidelis et al., 2012).

Vasodilator activity

The World Health Organisation estimates that hypertension affects approximately 25% of adults worldwide (Lawes et al., 2008). Hypertension is associated with severe complications, including end organ damage, arteriosclerosis, left ventricular (LV) hypertrophy and stroke (Kannel, 2000); it is imperative that additional treatments that also prevent cardiovascular complications are developed (Dolinsky et al., 2013).

The vasodilator effects of *O. semiserrata* stem hydroethanolic extract (OSE) and its EtAcO fraction (OSR) were evaluated with endothelium-intact aortic rings. The OSR produced more potent vasodilation (IC_{50} 3.5 µg/ml) than OSE (IC_{50} > 30 µg/ml). The OSR also presented a higher content of total proanthocyanidins (21.8 ± 1.5%) in comparison to OSE (6.5 ± 0.4%), thus leading the authors to suggest that compounds of this class play an important role in the vasorelaxation. The investigation of the vasodilatation mechanism of OSR revealed that its vasorelaxing effect was completely abolished by L-NAME (300 µM), a nitric oxide (NO) synthase inhibitor, but not by a muscarinic antagonist (atropine, 1 µM) nor by a cyclooxygenase inhibitor

(indomethacin, 10 µM). These findings showed that OSR, a proanthocyanidin-rich fraction of *O. semiserrata*, induces vasodilatation by a mechanism dependent on endothelium-derived factors, likely NO (Cortes et al., 2002). Posteriorly, leaves and stem hydroethanolic extracts from *O. castaneifolia*, *O. semisserrata* and *O. spectabilis* were assayed in aortic rings of rats pre-contracted with phenylephrine. Among these, only stem hydroethanolic extract from *O. semiserrata* produced significant vasodilating activity (63 ± 3%, n = 6), at 100 mg/ml (Valadares et al. 2003).

Antimalarial activity

Malaria is an infectious disease, of parasitic origin, that is a major cause of global morbidity and mortality. It is believed that about 300-500 million individuals contract the disease annually and more than 1 million people die of malaria every year (Murray et al., 2012). Plasmodium, the causative agent of malaria, is dependent on completing a complex cycle inside its vector, Anopheles mosquito, in order to be transmitted (Ghosh et al., 2000). However, the emergence and rapid spread of insecticide resistant mosquitoes and of drug-resistant Plasmodium parasites, combined with the lack of an effective vaccine, severely undermine current control efforts (Trape et al., 2011). Clearly, the available means to fight the disease are insufficient (Wang et al., 2013).

Estevam et al. (2005) reported the preliminary evaluation of *in vivo* antimalarial activity of the *n*-hexane, chloroform, ethyl acetate and hydromethanol extracts from the leaves of *Ouratea* nitida Aubl. using mice (*Mus musculus*) infected with *Plasmodium berghei*, NK-65 strains. Among them, only the hexane extract showed good activity against *Plasmodium berghei* of 47.87%, 77.95% and 51.04%, at tested doses of 250, 500 and 1000 mg/kg, respectively. Test results showed significant *in vivo* antimalarial activity, compared to the positive control chloroquine phosphate, whose activity against *P. berghei* was 100%. In contrast, increasing the concentration from 500 to 1000 mg/kg gave unsatisfactory results. The chromatographic purification of the hexane extract led to isolation of friedelin, β-amirin, 3,4-*seco*-friedelan-3-oic acid and tetracosan compounds.

Antimicrobial activity

Crude extracts from plants used in folk medicine have been screened *in vitro* by many research groups for antibacterial properties. The antibacterial activity of flavonoids is increasingly documented (Cushnie and Lamb, 2005).

Compounds sulcatone A (57) and 3-hydroxy-2,3-dihydroapigenyl-[C-4'-O→C-3']-dihydrokaempferol (58), obtained from the aerial parts of *O. sulcata*, displayed activity against *Staphylococcus aureus* (MIC value of 12.50 µg/ml at 57 and 8.12 µg/ml at 58) and *Bacillus subtilis* (MIC value of 8.51µg/ml at 57 and 10.05 µg/ml at 58), Gram positive bacterium. These activities were almost equivalent to those demonstrated by streptomycin sulphate (MIC value of 6.25µg/ml at 57 and 0.85 µg/ml at 58). However, none of these compounds were active against *Vibrio anguillarium* (Gram positive bacterium) or *Escherichia coli* (Gram negative bacterium) in agar diffusion assays (Pegnyemb et al., 2005). Biflavones heveaflavone, 7'',4'''-dimethylamentoflavone, podocarpusflavone-A and amentoflavone, obtained from leaves of *O. multiflora*, showed weak activity against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* at the 10 µg/ml concentration, and only compounds heveaflavone and podocarpusflavone-A inhibited the growth of S. aureus at a concentration of 0.5 µg/ml. The compounds tested showed moderate inhibition (zone inhibition = 7.0-10.0 mm), compared to streptomycin sulphate (zone inhibition = 30-35 mm), used as the reference antibiotic, at 5 µg/ml (Carbonezi et al., 2007).

Ouratea extracts display moderate or no inhibition against several species of Gram-positive cocci bacteria (*Staphylococcus aureus*, *S. epidermidis*, *S. saprophyticus*, *Enterococcus* sp., En. hirae,), Gram-negative bacilli (*Escherichia coli, Klebsiella pneumonia*, *Serratia marsescens*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) or fungi (*Candida* spp., *Cryptococcus* neoformans sero D, *Aspergillus* spp., *Tricophyton* spp.) in disk diffusion assays and with a final concentration between 2 and 1024 µg/ml. The methanolic extracts from leaves of *O. sulcata* showed activity against *Staphylococcus* spp., with inhibition zones of 10-13 mm, whereas similar extracts from *O. flava* and *O. elongata* only showed activity against *Candida albicans*, with inhibition zones of 7-13 and 7-10 mm, respectively (Gangoué-Piéboji et al., 2006). The crude CH_2Cl_2:MeOH (1:1) extract from roots of *O. turnarea* showed only moderate activity against Gram-positive cocci. The minimal inhibitory concentration of these crude extracts varied from 2.5 to 5 mg/ml. Serotobenine, isolated from crude extract of *O. turnarea*, was evaluated by the same antimicrobial assay and did not exhibit any activity for any bacterial strains tested (Zintchem et al., 2008). The antimicrobial activities of crude MeOH extracts of *O. zenkeri* and *O. turnerae* leaves were also examined by Mbing et al. (2009) and both extracts exhibited moderate antimicrobial activity against these microorganisms.

Recently, Bikobo et al. (2009) evaluated and compared the antimicrobial properties of methanol extracts of *Ouratea sulcata*, *O. flava*, *O. elongata*, *O. reticulata* and *O. staudtii*. Again, it was observed that the activity of *Ouratea* extracts was more pronounced against Gram-positive bacteria and yeast than Gram-negative bacteria, for which no activity was observed. The most active antimicrobial plants were *O. sulcata* and *O. flava*. Some biflavonoids evaluated were also most active against gram positive compared to gram negative bacteria.

Aflatoxins are secondary metabolites of *Aspergillus flavus* and *A. parasiticus*, been shown to be toxigenic, carcinogenic, mutagenic, and teratogenic to different animal species (Fan and Chen, 1999). The biflavonoids 6,6"-bigenkwanin (48); tetramethoxybigenkwanin (**48a**); amenthoflavone (**32**), and 7,7"-di-O-methylagathisflavone (**45**) obtained from *O. spectabilis*, *O. multiflora* and *O. parviflora* have shown an inhibitory effect on the aflatoxin biosynthesis that are secondary metabolites of *Aspergillus flavus*. *A. flavus* used as a control produced 188.6 µg/ml of AFB1 and 12.58 µg/ml of AFB2, while the fungus treated with biflavonoids **48**, **48a**, **32** and **45** at 5 µg/ml concentration produced 56.58, 42.65, 37.42 and 45.19 µg/ml of AFB1, and 2.38, 2.87, 1.88 and 3.17 µg/ml of AFB2, respectively. At a concentration of 10 µg/ml, the results obtained were 22.58, 22.29, 18.41 and 27.56 µg/ml of AFB1 and

2.34, 0.75, 1.11 and 1.55 µg/ml of AFB2 for compounds **48**, **48a**, **32** and **45**, respectively. The cytotoxicity of (**45**), (**48**) and (**48a**) was also evaluated for SIRC cell line by spectrophotometric measurements, to determine the concentrations of substances that inhibited the absorbance to 50% of the control level (IC_{50}). Compounds **45**, **48** and **48a** presented IC_{50} of 426.74 ± 22.05, 381.9 ± 22.29 and 359.7 ± 24.25 mg/ml respectively (Gonçalez et al., 2001).

Antioxidant activities

The antioxidant activities of biflavones **32**, **35**, **37** and **40** from *O. multiflora* were tested toward DPPH radicals. Compound **32** showed moderate scavenging activity (IC_{50} 18.5 µg/ml) in this test, while **35**, **37** and **40** showed weak scavenging activity, which confirms the dependence of the antioxidant activity on the number of free phenol groups of the tested compounds (Carbonezi et al., 2007).

Discussion

The *Ouratea* genus has been characterised to be a good source of flavonoids and biflavonoids and some species are used in folk medicine, mainly for the treatment of inflammatory and infectious diseases. It has been established that leaves extracts of *O. parviflora* are important to attenuate the oxidative damage caused by ROS (Carbonari et al., 2006) and *O. semisserrata* has shown lipoxygenase inhibiting potential (Braga et al., 2000); thus these extracts can be considered as phytotherapeutics for the treatment of inflammation. These results have contributed for confirmation of the anti-inflammatory effects of *Ouratea* species in the traditional medicine. For example, leaves extracts of *O. elongata*, *O. sulcata*, *O. flava* and *O. parviflora* are used in the treatment of diseases such as rheumatism, sprains, arthritic disorders and toothache (Carbonari et al., 2006; Bouquet, 1969; Pegnyemb et al., 2005; Gangoué-Piéboji et al. 2006; Mbing et al., 2003a).

The use of plants from this genus in respiratory tract infections, dysentery, diarrhoea, erysipelas and uterine wounds can be justified because of the antimicrobial and antiviral effects of the extracts or phytochemicals. Although some flavonoids and extracts of *Ouratea* have been shown to be more active against Gram-positive bacteria than Gram-negative bacteria (Bikobo et al. 2009), other flavonoids, such as catechins, also appear to have greater activity against Gram-positive than Gram-negative bacteria. Ikigai and colleagues (Ikigai et al., 1993) have demonstrated that epigallocatechin gallate induced the leakage of small molecules from the intraliposomal space of liposomes (used as model bacterial membranes). Ikigai et al. suggested that the low catechin susceptibility of Gram-negative bacteria may be, at least partially, attributable to the presence of lipopolysaccharides in the membrane bilayer acting as a barrier (Ikigai et al., 1993; Cushnie et al., 2005). It is believed that, as for the catechins, the flavonoids tested are less susceptible to Gram-negative bacteria due to the presence of the membrane bilayer. No study of the antibacterial mechanism of action of the *Ouratea* flavonoids has been published to date. However, these compounds still have important roles in traditional medicine. Furthermore, flavonoids or extracts containing flavonoids, when used along with conventional antibiotics against quite resistant bacterial strains, exert a significant synergistic effect, as described in the literature (Stepanovic et al., 2003).

Notable antiviral (against HSV, Parainfluenza-3 and Poliomyelitis-1) and antifungal (inhibitory effect on the aflatoxin biosynthesis in the Aspergillus flavus and A. parasiticus) activities were observed for biflavonoids and extracts from *Ouratea* species (Roming et al., 1992; Gonçalez et al., 2001). Biflavonoids from plants of the *Ouratea* genus are good candidates for research into the mechanisms of antiviral action; additional studies are needed as they may help in the development of antiviral therapy.

Several relevant activities have been described for *Ouratea* species that are not related to the traditional uses, such as anticancer (Oliveira et al., 1972; Daniel et al., 2007) and chemopreventive (Fidelis et al., 2012), antimalarial (Estevam et al. 2005), hepatoprotective (Carbonari et al., 2006) and vasorelaxant or anti-hypertensive activities (Valadares et al. 2003).

It remains surprising that despite the potent vasorelaxant effect found for extracts of *O. semisserrata*, any traditional uses were related to treat hypertensive diseases. Thus, additional studies would be necessary for the development of phytotherapeutics obtained from *Ouratea* extracts, such as *O. semisserrata* and *O. hexasperma*.

Other activities requiring attention are those that involve the inhibition of enzymes by flavonoids. Good results were found for aldose reductase inhibition using biflavonoids from *O. spectabilis* (Felício et al., 1995). Biflavones of *O. hexasperma* showed high inhibition of DNA-topoisomerase I and II (Grynberg et al., 2002). It is possible, therefore, that the mechanisms of action involved in the antiviral and anticancer activities can be related to the vital enzymatic inhibition of cellular metabolism.

There is strong evidence in the literature that has led us to believe that biflavonoids from *Ouratea*, as well as several polyphenols of plants, have the ability to modulate target enzymes (Quideau et al., 2011). Thus, these compounds may exert their protective actions against several diseases.

Conclusion

The genus *Ouratea* presents large chemical diversity, comprising mainly flavonoids and biflavonoids. The more abundant biflavonoids, such as amentoflavone and agathisflavone, have been considered chemotaxonomic markers of this genus. Of 300 species, only 25 have been examined. It was perceived that extensive research work had been done with some species of this genus; however, a large number of species are still chemically and/or pharmacologically unknown. While this review has attempted to unite the relevant information for these species, the bioactive profile of *Ouratea* species and its flavonoids as the main bioactive compound, clearly suggests future research priorities. Convincing ethnopharmacological evidence is presented alluding to the use of leaves from *Ouratea* species for rheumatism, sprains, arthritic disorders

and toothaches, but there has been no research regarding this information. The anti-inflammatory activity remains poorly explored, both *in vivo* and *in vitro*; however, the results found were promising. Flavonoids are well known for their biological properties and although a suite of compounds belonging to this class of phytochemicals, such as biflavonoids, has been isolated from the *Ouratea* genus, only a few have been subjected to pharmacological assays. Several studies have revealed the potential of these plants and their constituents for anticancer, antimalarial, antiviral, antimicrobial and vasodilating activities. In our opinion, the presence of biologically active biflavonoids makes the species of the *Ouratea* genus extremely promising, considering specially that the time of action of dimers ais longer than that of monomers, as cited by Iwu M.M. (1986) concering the biflavanones of *Garcinia*. Moreover, these compounds can be used as models to attain more potent and effective synthetic derivatives. Taken together, all of the results compiled here indicate that the genus may play an important role in the discovery of new medicinal agents.

Authors' contributions

QCF contributed with data collection and writing of the manuscript. TANR and MFA contributed with data collection and format of the manuscript. MGC suggested the manuscript outline, participated in data collection, writing of the manuscript and final editing of the manuscript. All the authors contributed to the critical reading of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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