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Butyrylcholinsterase inhibitors from two *Ficus* species (Moraceae)

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementiaand mainly afflict people over 65 years of age. AD is characterized by a progressive memory loss that leads to a profound emotional disturbance in later stages.As no safe and effective drug is yet available for the treatment of AD,secondary metabolites from plants may be instrumental in meeting this challenge. From this work, 29 compounds were isolated and fully characterized and six of them:*β*-isolutéon (11), dehydroferreirin (12),lupiwighteon hydrate (13),Aviprin (24), blumenol A (26)and*p*-menthane-3,6-diol(27) have never been previously reported from the genus *Ficus*. This study also reports the complete ^{1}H NMR assignment of lupiwighteon hydrate (13) for the first time.All the isolated compounds were purified through usual chromatographic methods and their structures established by the means of NMR data. Some isolated compounds as well as methanolic crude extracts were evaluated for their inhibitory potential against both acetyl- and butyrylcholinesterase enzymes by Ellman method. None of the crude methanolic extract showed response against tested enzymes. However, the ability of some isoflavonoids and coumarin from *Ficus pumila* Linn and *Ficus thonningii* Blume to inhibit cholinesterase has been evaluated.Alpinumisoflavon (5), lupiwighteonhydrate (13), two isoflavones and aviprin(24), a furano-coumarin showed good inhibitory activities against butyrylcholinesterase but not against acetylcholinesterase using eserin/galantamine as positive controle. These results are in agreement with the ethnobotanical uses of these plants and indicated that this activity could contribute significantly to the pharmacological properties of these species.

Keywords: Ficus, Moraceae, Butyrylcholinesterase Inhibition, Alzheimer's disease.

1. INTRODUCTION

Alzheimer's disease (AD) is one of the most widespread neurodegenerative diseases that involve dementia and mainly afflict people over 65 years of age. There are estimated of about 36 million people living with dementia worldwide and the number is expected to be increased up to 66 million in 2030, and is projected to increase to 115 million by 2050[1-3]. Nearly 66% cases of dementia carriers are living in lowand middle-income countries [1, 4].The therapy ofearly and moderate stages symptomatic treatment of AD is mainly based on cholinesterase inhibitorsto enhance central cholinergic transmission and to improve cognition and behavior[5, 6].

Cholinesterases are a group of serine hydrolases that split the neurotransmitter acetylcholine (ACh) and terminate its action.There are two principal cholinesterases in the human brain, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE is membrane bound predominantly on presynaptic cholinergic neurons, but is also on postsynaptic cholinoceptive neurons [7]. BuChE has a neuroglial distribution [8, 9]. The physiological role of AChE is to terminate the synaptic action of Ach through catalytic hydrolysis. ACh is hydrolyzed by both AChE and BuChE, but AChE catalyzes the hydrolysis of ACh much more efficiently than BuChE[10]. The physiological role of BuChE is poorly understood, particularly in the central nervous system. Recent attention has focused on this enigmatic enzyme and its possible relevance in the treatment of AD [11-13].Butyrylcholinesterase (BuChE) is of pharmacological and toxicological importance, because it catalyzes cleavage ester-containing drugs. Compared to AChE, the importanace of BChE is not well understood [6, 14, 15].

Recent reports on medicinal plants showed that about 63% of low molecular drugs developed from 1981 to 2006, were natural products. These reports suggested that natural products have strong potential to be developed into biologically active compounds with anti-AD activity [16].Traditionally, medical plants have been used to enhance memory and to alleviate other symptoms associated with AD. The biologically active plant-derived substances that may be considered as a source of new anticholinesterase

drugs come from different classes of compounds and are characterized by the diversity of their structures. The majority of bioactive substances inhibiting cholinesterase are in doles, steroids, piperidines phenyl-propanoids (furano-coumarins, xantones, and flavonoids) and diterpenes[17].

Moraceae species are well known for their acetyl- and/or butyrylcholinesterase inhibitory activity [18-20]. In this study, two plants namely, *Ficuspumila* Linn and *Ficus thonningii* Blume of the family Moraceae, traditionally used in African folk medicine for the treatment of several ailments such as mental illnesses, age-related brain disorder, diarrhea, urinary tract infections, diabetes mellitus, respiratory infections and other common diseases, were selectedfor our ongoing research for new bioactive compounds from Cameroonian medicinal plants of the *Ficus* genus [21-25]. In this present study, extracts and some chemical constituents of *Ficus pumila* Linn and *Ficus thonningii* Blume were evaluated for their potential cholinesterase inhibitory activity. The inhibition effects of these three compounds indicate that they could contribute significantly to the research of new therapeutics against Alzheimer's disease. It also report the isolation of 29 compounds among which six are described for the first time from the genus *Ficus*. Here in,is reports for the first time the complete ^{1}H NMR assignment of lupiwighteon hydrate (13).

2. MATERIALS AND METHODS

2.1 Plant material

F. thonningii and *F. pumila* were collected in August 2012 at Mile 5, Nkwen, in Bamenda, in the North-West region and Ngoa-ekele, in the Center region of Cameroon, respectively. Both plants were identified by Mr. NANA Victor, taxonomist at the National Herbarium of Cameroon (NHC), where vouchers numbers of specimens are submitted (*F. thonningii* HNC 44042; *F. pumila* HNC 49523).

2.2 Preparation of sample and extraction

The freshly collected plant materials were chopped and air dried. The air dried samples were cut into small pieces and ground into fine powder using a dry grinder. Each plant was extracted separately with MeOH (10 Lx 3) for a period of 72 hours at room temperature (25˚C), filtered, evaporated and concentrated under reduced temperature and pressure to viscous crude extracts. Obtained compounds were isolated using conventional separation methods. Structures have been elucidated by usual spectroscopic methods (UV, IR, MS, 1D and 2D NMR) and by comparison of some physical and spectral data with those described in the literature. From this work, 29 compounds were isolated and fully characterized.

2.3 Determination of *in vitro* acetylcholinesterase- (AChE) and butyrylcholinesterase- (BChE) inhibitory activity

AChE and BChE inhibitory activity was measured by the spectrophotometric method developed by Ellman *et al*. in 1961 [26]. AChE from electric eel and BChE from horse serum were used, while acetylthiocholine iodide and butyrylthiocholine chloride were employed as substrates of the reaction.

The reaction mixture containing 100 mM sodium phosphate buffer (pH 8, 150 µL), DTNB (10 µL), test compound solution (10 µL) and butyrylcholinesterase solution (20 µL) was mixed and incubated for 15 minutes (25 °C). The reaction was then initiated by the addition of butyrylthiocholine (10 µL). The hydrolysis of butyrylthiocholine was monitored by the formation of yellow 5-thio-2-nitrobenzoate anions as the result of the reaction of DTNB (5,5'-dithiobis(2-nitrobenzoic)acid) with thiocholine, released by the enzymatic hydrolysis of butyrylthiocholine at a wavelength of 412 nm (15 min.). Test compounds and the positive control (serine/galantamine) were dissolved in EtOH. All the reactions were performed in triplicate in 96-well micro-titre plates in Spectra Max 340 (Molecular Devices, U.S.A.).

The percentage (%) inhibition was calculated as follows (E – S)/E × 100, where E is the activity of the enzyme without test compound and S is the activity of enzyme with test compound.Each sample was analyzed in eight repeats.

2.4 Determination of IC_{50} values

The concentrations of test compound and positive control that inhibited the hydrolysis of substrate (butyrylthiocholine) by 50 % (IC_{50}) were determined by monitoring the effect of various concentrations of these compounds in the inhibition value assays. The IC_{50}values were then calculated as standard mean error of five assays using the EZ-Fit Enzyme Kinetics program (Perrella Scientific Inc., Amherst, MA, U.S.A.).

3. RESULTS

3.1 Isolated compounds

Using various isolation methods (Silica gel, *Sephadex LH-20*, *RP C18etc.*), twenty nine compounds (Fig. 1) were obtained from methanolic extract of *F. thonningii* and *F. pumila* including seventeen flavonoids: naringenin (1), (+)-afzelechin (2), (+)-catechin (3), rutin (4), alpimumisoflavon (5), hydroxyalpinumisoflavon (6), wighteon (7), luteon (8), dihydroquercetin (9), (+)-aromadendrin (10), *β*-isoluteon (11), dehydroferreirin (12), lupiwighteon hydrate (13), thonningiisoflavone (14), shuterin (15), thonningiol (16), conrauiflavonol (17); four triterpenes: *β*-amyrin acetate (18), friedelin (19), lupeol acetate (20), lupeolhexanoate (21); three coumarins: psoralen (22), bergapten (23), aviprin (24); a benzoic acid derivative: vanilic acid (25) and one ionone: blumenol A (26), one monoterpene: *p*-menthane-3,6-diol (27); along with two sterol: a mixture of *β*-sitosterol and stigma sterol and, *β*-sitosterolglucoside. Compounds 11, 12, 13, 24, 26 and 27 are reported from the genus *Ficus* for the first time.Also, the complete ^{1}H NMR assignment of lupiwighteon hydrate (13) is established for the first time (Table 1).The structures of all the compounds were confirmed on the basis of spectroscopic data and those available in the literature (Table 1 and 2).

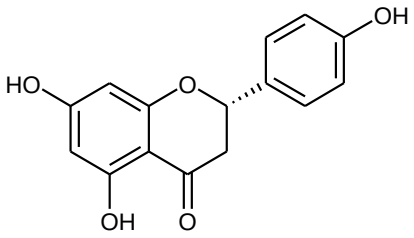
Table 1: ^{1}H NMR of **5** and **13** in (DMSO-d_6, 500 MHz) and **24** in ($CDCl_3$, 500 MHz)

Position	5	13	24
		δ_H (m, *J* (Hz))	
2	8.36 (1H, s)	8.36 (1H, s)	-
3	-	-	6.29 (1H, d, *J* = 10.0 Hz)
4	-	-	8.16 (1H, d, *J* = 9.5 Hz)
5	OH 13.37 (1H, s)	OH12.90 (1H, s)	-
6	-	6.30 (1H, s)	-
7	-	-	-
8	6.49 (1H, s)	-	7.17 (1H, s)
9	-	-	-
10	-	-	-
1′	-	-	
2′	7.37 (2H, d, *J* = 8.5 Hz)	7.37 (2H, dd, J = 9.0; 2.5 Hz)	7.59 (1H, d, *J* = 2.0 Hz)
3′	6.81 (2H, d, *J* = 9.0 Hz)	6.80 (2H, dd, J = 9,0; 2.5 Hz)	6.97 (1H, d, *J* = 2.0 Hz)
4′	OH 9.60 (1H, sl)	OH9.55 (1H, sl)	-
5′	6.81 (2H, d, *J* = 9.0 Hz)	6.80 (2H, dd, J = 9.0; 2.5 Hz)	-
6′	7.37 (2H, d, *J* = 8.5 Hz)	7.37 (2H, dd, J = 9.0; 2.5 Hz)	-
2″	-	2.67 (2H, ddd, *J* = 8.5; 5.0; 3.5 Hz)	4.43 (1H, dd, *J* = 10.0; 8.0 Hz) 4.52 (1H, dd, *J* = 10.0; 2.5 Hz)
3″	5.80 (1H, d, *J* = 10.5 Hz)	1.52 (2H, ddd, *J* = 8.5; 5.0; 3.5 Hz)	3.89 (1H, dd, *J* = 8.0; 3.0 Hz) OH 2.77 (1H, sl)
4″	6.61 (1H, d, *J* = 10.0 Hz)	-	OH 2.10 (1H, sl)
5″	1.42 (3H, s)	1.16 (3H, s)	1.34 (3H, s)
6″	1.42 (3H, s)	1.16 (3H, s)	1.30 (3H, s)

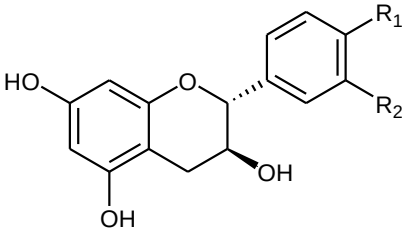
Table 2: ^{13}C NMR of **5** and **13** in (DMSO-d_6, 125 MHz) and **24**in($CDCl_3$, 125 MHz)

Position	5	24	13
		δ_C(m)	
2	154.2 d	161.0 s	154.1 d
3	122.4 s	113.2 d	121.3 s
4	180.5 s	138.9 d	180.6 s
5	156.7 s	148.5 s	159.4 s
6	105.4 s	114.3 s	98.5 s
7	158.8 s	158.1 s	161.8 s
8	94.6 d	95.0 d	107.2 s
9	157.5 s	152.6 s	154.9 s
10	104.7 s	107.4 s	104.4 s
1′	121.0 s	-	121.8 s
2′	130.1 d	145.3 d	130.1 d
3′	115.0 d	104.7 d	115.0 d
4′	156.0 s	-	157.3 s
5′	115.0 d	-	115.0 d
6′	130.1 d	-	130.1 d
2″	78.1 s	74.5 t	17.2 t
3″	129.1 d	76.5 d	42.8 t
4″	114.5 d	71.7 q	68.9 s
5″	27.8 q	26.7 q	29,1 q
6″	27.8 q	25.2 q	17.2 q

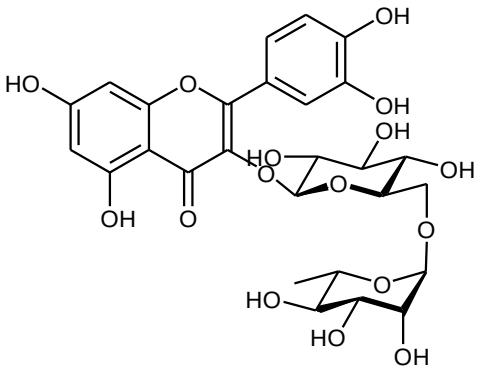
Flavonoids



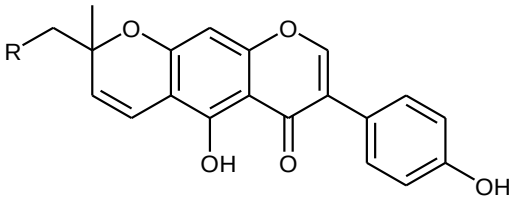
Naringenin (1)



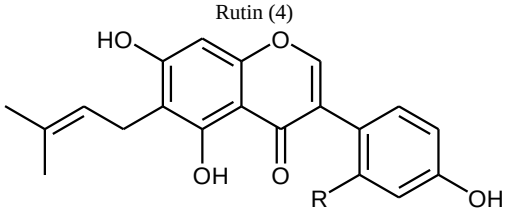
R_1 = OH; R_2 = H (+)-Afzelechin (2)
R_1 = OH; R_2 = OH (+)-Catechin (3)



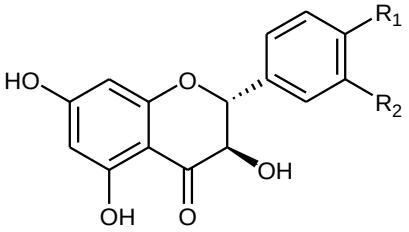
Rutin (4)



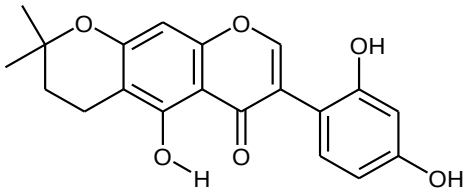
R = H Alpinumisoflavon (5)
R = OH Hydroxyalpinumisoflavon (6)



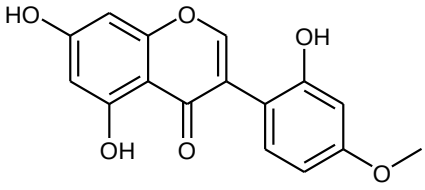
R = H Wighteon (7)
R = OH Luteon (8)



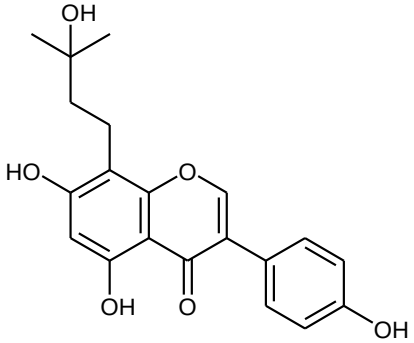
R_1 = OH; R_2 = H Dihydroquercetin (9)
R_1 = OH; R_2 = OH (+)-Aromadendrin (10)



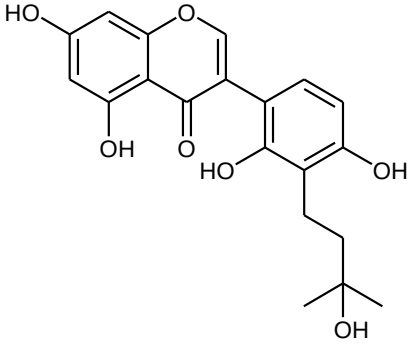
β-isoluteon (11)



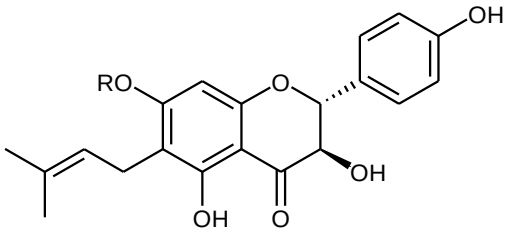
Dehydroferreirin (12)



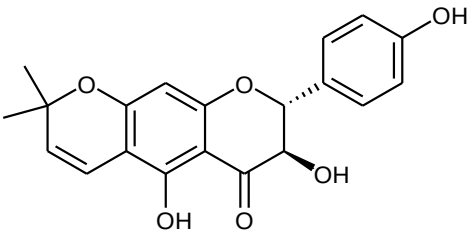
Lupiwighteon hydrate (13)



Thonningiisoflavone (14)

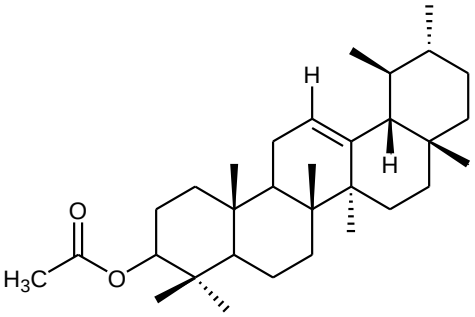


R = H (+)-Shuterin (15)
R = CH_3Thonningiol (16)

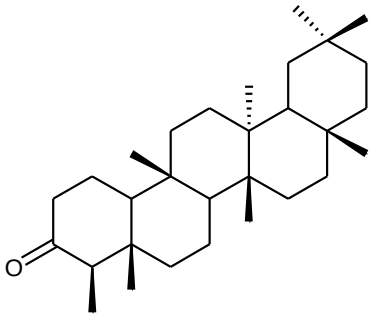


Conrauiflavonol (17)

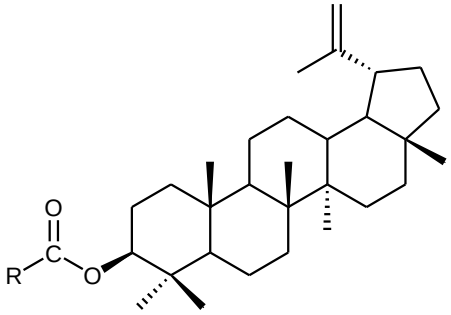
Triterpenes



β-amyrin acetate (18)

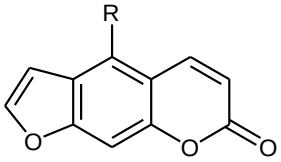


Friedelin (19)

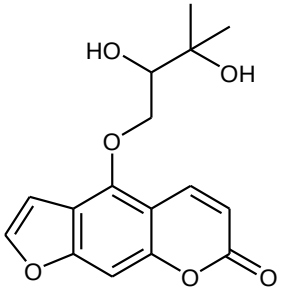


R = CH_3Lupeol acetate (20)
R = -$(CH_2)_4CH_3$Lupeolhexanoate (21)

Coumarins

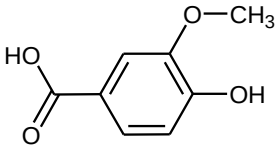


R = H Psoralen (22)
R = -OCH_3Bergapten (23)



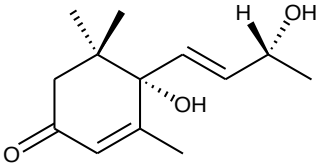
Aviprin (24)

Benzoic acid derivative



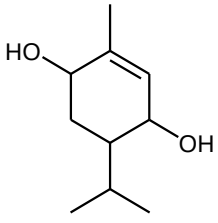
Vanilic acid (25)

Ionone



Blumenol A (26)

Monoterpene



p-menthane-3,6-diol (27)

3.2 Acetylcholinesterase inhibition activity

Cholinesterases are enzymes that share extensive sequence homology and distinct substrate specificity and inhibition sensitivity. Cholinesterases are potent target for the symptomatic treatment of Alzheimer's disease and related dementia. For this bioactivity, the preliminary screening showed that all the crude extracts of different parts of the two species were not active. However, three of the isolated compounds (5, 13 and 24) demonstrated good activity with IC_{50} value of 34.1 ± 0.21, 82.3 ± 0.6 and 53.5 ± 0.9µMrespectively (Table 3). Eserin (IC_{50} = 0.82 ± 0.001) and galantamine (IC_{50} = 75.5 ± 1.1) were used as positive control.

Table 3: inhibition of AChE and BChE enzymes by methanolic extracts and isolated compounds from two *Ficus* species.

Compounds	IC_{50} ± SEM (µM)	
	AChE	BChE
1	-	-
5	-	34.1 ± 0.21
10	-	-
12	-	-
13	-	82.3 ± 0.6
24	-	53.5 ± 0.9
Eserin*	0.04 ± 0.0001	0.82 ± 0.001
Galantamine*	99.8 ± 0.31	75.5 ± 1.1
Extracts		
FTRE	-	-
FTSB	-	-
FTF	-	-
FPSB	-	-
FPF	-	-

* Standard inhibitory
Values expressed are means±S.D. of three parallel measurements. ($p<0.05$)
\- : non active
FTRE : *F. thonningii* roots extract
FTSB : *F. thonningii* stem back extract
FTF : *F. thonningii* figs extract
FPSB : *F.pumila* stem back extract
FPF : *F.pumila*figs extract

4. DISCUSSION

It has been mentioned in actual research that natural products constitutes an enriched source of compounds with anticholinesterase activity. Butyrylcholinesterase (BChE) inhibition is an effective tool for the treatment of Alzheimer's disease(AD) and related dementias. In this study, extracts and some of the isolated compounds were tested for their ability to inhibit the cholinesterase using eserin and galantamine as positive control. All the extracts were found to be inactive. However, three of the compounds tested (5, 13 and 24) for both AchE and BChE showed anti-cholinesterasic activity only on BChEat the same concentration as the reference compounds physostigmine and galantamine.

Eserin (physostigmine) is a natural alkaloid and the first inhibitor of AChE that has been tested in the treatment of Alzheimer's disease,but clinical use may be limited by its short half-life, which would require multiple daily dosing.

Its affinity for acetylcholinesterase is ten thousand times higher than that of acetylcholine which makes it a very powerful parasymphatomimetic leading to bradycardia, vomiting and respiratory paralysis[27]. Unlike eserine, galanthamine has a dual mechanism of action: in addition to inhibiting AChE, it causes allosteric modulation of presynaptic nicotinic receptors, increasing the release of neuromediators. Recent studies have also shown a favorable effect of galanthamine on the production of APPα neuroprotective peptide. Its dual action in both AChE and nAChR is an advantage and unlike other marketed drugs that inhibit AChE[28,29].

In general, compared to galantamine, the three isolated compounds showed good BChE inhibitory activity and were inactive against AChE.

The results of this work showed that the three active compounds are less active than eserine and more active than galantamine. Owing from the fact that eserine have a very bad side effect and could not be easely used for the treatment of AD, Alpinumisoflavon, lupiwighteonhydrate and aviprin present a promising issue which may leadto discovery of new drugs for the treatment of AD. These results are also in agreement with some previous report on the ability of the genus *Ficus* in the treatment of mental illnesses and dementia and, the butyrylcholinesterase inhibitory effects of some flavonoids[30, 31].

5. CONCLUSION

In the present study, cholinesterase enzyme inhibitor activities of extracts and some bioactive constituents from *F. pumila* and *F. thonningii* were investigated.Three of the isolated compounds showed good inhibitory activities against butyrylcholinesterase but not against acetylcholinesterase using eserin/galantamine as positive controle. These findings suggest that the two *Ficus* species reported in the literature for the treatment of mental diseases possess a googanticholinesterase activity. Therefore, they could have favourable pharmacological profile in the treatment of Alzheimer's disease. Since butyrylcholine plays a vital role in cognitive function including learning and progressive memory loses. Plant derived pharmacological agents may provide an attractive therapeutic option in future for several pathological conditions especially the neurodegenerative diseases due to their anticholinesterase, antioxidant and radical scavenging properties.Therefore, these results could be considered for further studies in thetreatment of AD and other dementia diseases.

Furthermore,29 compounds were isolated and fully characterized and six of them are reported from the genus *Ficus* for the first time. This study also reports the complete ^{1}H NMR assignment of lupiwighteon hydrate for the first time.

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