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Ubiquitous Ursolic Acid: A Potential Pentacyclic Triterpene Natural Product.

Ibrahim T Babalola [1,2*], Francis O. Shode [2]

1. Department. of Chemistry, Faculty of Science, Yobe State University, PMB 1144 Damaturu, Nigeria [E-mail: chemibrabal@gmail.com; Tel: +234(0)8035879874]
2. Department of Chemistry, Faculty of Sciences and Agriculture, University of Zululand, Private Bag X1001, KwaDlangezwa 3886, Republic of South Africa and Research, Innovation & Development Director of Life-Promoters Biosciences (Pty) Ltd, 5 Ferrara Gardens, Westville North 3629, South Africa.

There is an unprecedented growing interest in natural triterpenes in the last few decades due to the discovery of their potential biological and pharmacological activities. Ursolic acid (3β-hydroxyurs-12-en-28-oic) (UA) (**4**) is a pentacyclic triterpene, occurring in many plant parts including fruits and seeds. This paper reviews several studies on the *in vitro* and *in vivo* pharmacological activities of UA (**4**). This review brings to limelight sources and the beneficial potentials of UA (**4**) in foods, cosmetics and medicine.

Keyword: Natural Products, Pentacyclic Triterpene, Ursolic Acid, Health Benefit, Pharmacological Activity

1. Introduction

Secondary metabolites are natural products that often have an ecological role in regulating the interactions between plants and their environment. They can be defensive substances such as phytoalexins and phytoanticipins, anti-feedants, attractants, and pheromones [1]. The importance of plant secondary metabolites in medicine, agriculture and industry has led to numerous studies on the synthesis, biosynthesis and biological activity of these substances. It has been estimated that over 40% of medicines have their origins in these active natural products [2]. A prominent group of natural products is the terpenes and their derivatives.

A group of terpenes that is attracting much attention lately is the pentacyclic triterpenoids (PCTs). PCTs are a class of C_{30} isoprenoid compounds occurring widely in plants. These compounds are produced biosynthetically by the folding and cyclization of squalene which leads to the dammarenyl ring system (I) (Figure 1), which has a slightly different stereochemistry and ring structure from that of major sterols [3]. Biosynthetically, dammarenyl (I) undergoes ring expansion and additional cyclization to form the characteristic fifth ring found in lupeol (**1**) (Figure 1), α-amyrin (**2**) and β-amyrin (**3**) skeletons (Figure 2). Ursolic acid (**4**) contains the α-amyrin skeleton; its C_{30} isomer, β-amyrin is found in oleanolic acid (**5**). Review of scientific literature dealing with triterpenoids' isolation and identification from natural sources has been reported[4].

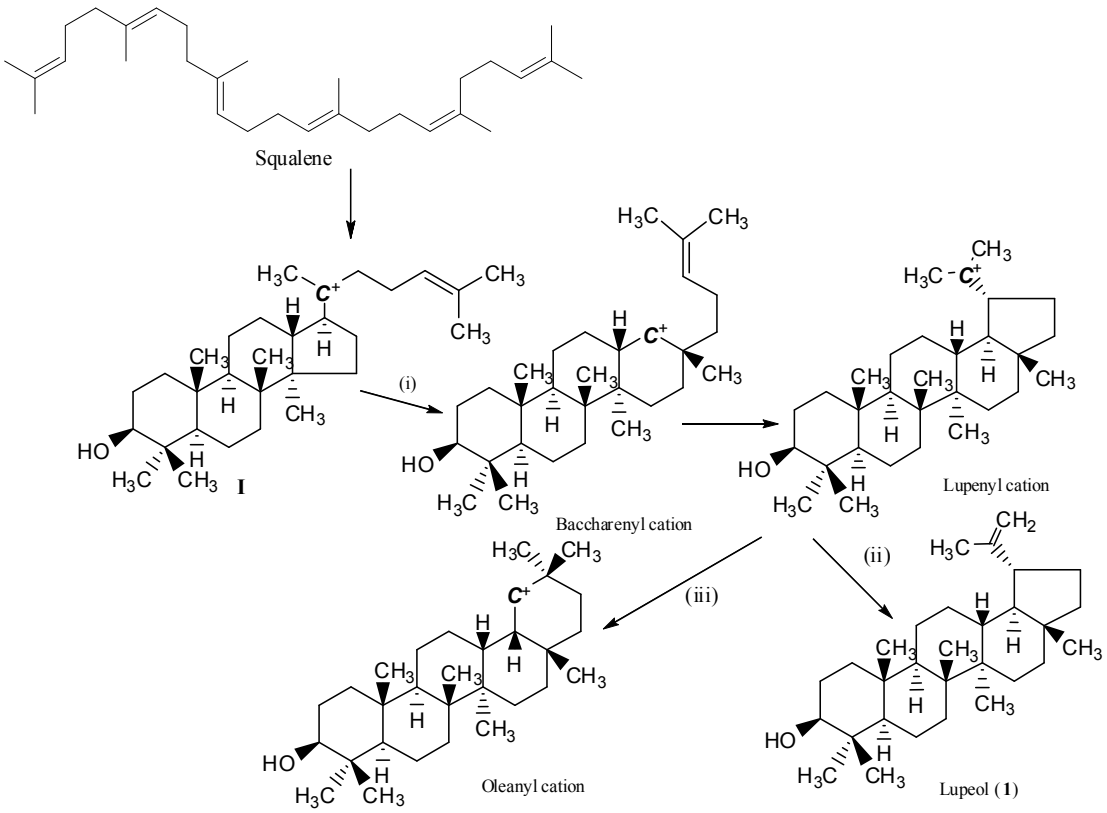


Fig 1: Biosynthesis of dammarenyl cation (**I**), oleanyl cation, lupenyl cation and lupeol (**1**).

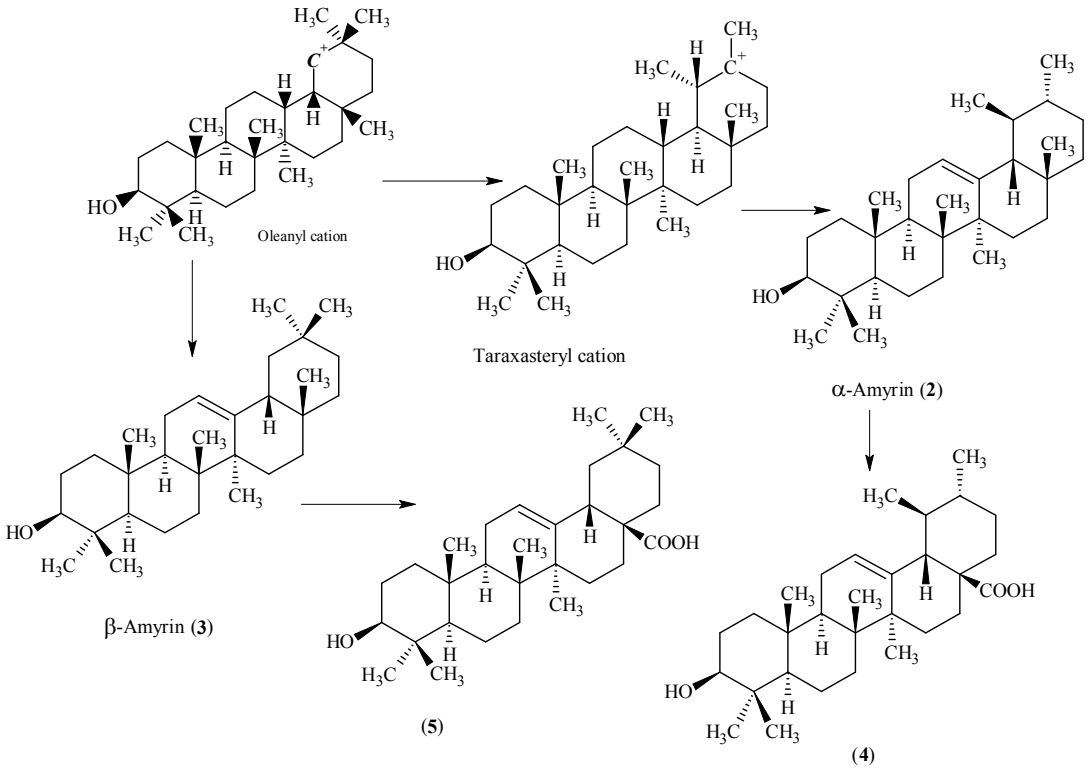


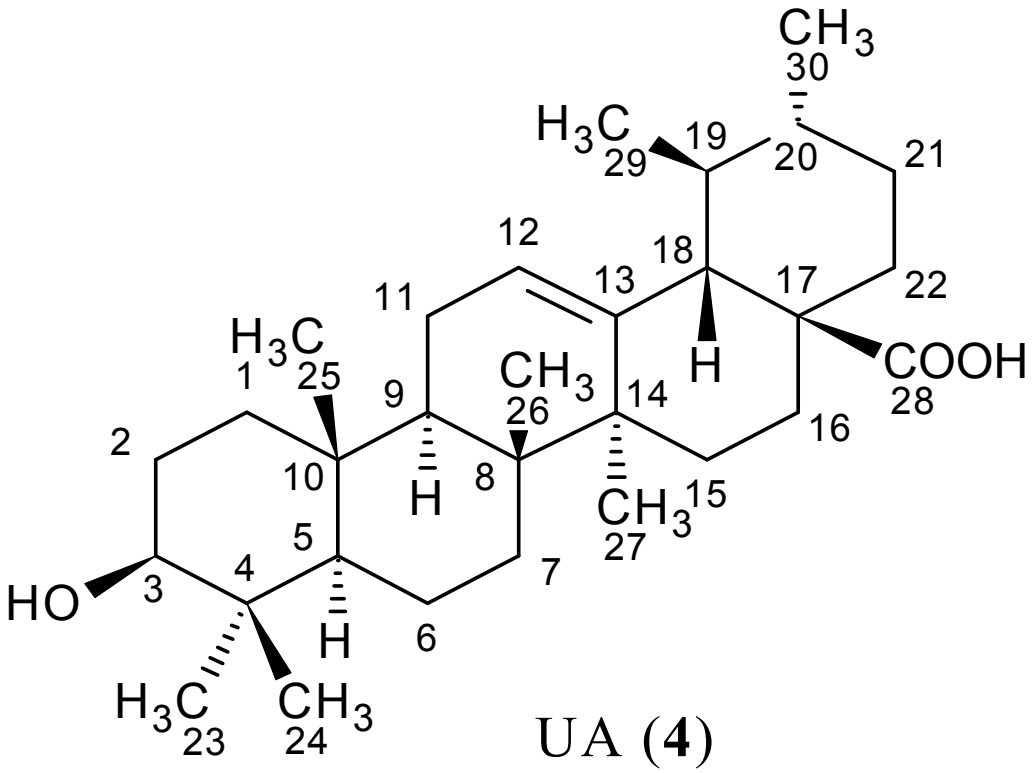
Fig 2: Biosynthesis of ursolic acid (**4**) and oleanolic acid (**5**) from oleanyl cation.

UA (**4**) is present in a wide variety of plants in the form of a free acid or an aglycone of triterpene saponins. Chemically, UA (**4**) is known as merotaine. It is also known as urson, prunol, micromerol, and malol, which occurs as a white, light green, yellow and sometimes creamy yellow depending on the source.

1.2 Chemical Structure and Analysis

The chemical formula of UA (**4**) (Figure 3) is $C_{30}H_{48}O_3$ and its melting point is 283-285°C. Properties computed from the structure of ursolic acid show that it has a molecular weight of 456.7g/mol. Its UV spectrum shows strong absorption bands at 474, 442, and 422 nm and the IR (ATR, cm^{-1}) spectrum shows strong absorptions at 3562 (OH alcohol), 2937 (OH acid), 2865 (C=C) and 1698 (C=O) [5], [6] . Study conducted by Gnoatto group using high resolution electrospray mass spectra in the positive ion mode observed m/z 455.3522$[M+H]^+$ [7].

The ^{13}C-NMR spectrum of UA (**4**) (Table 1) shows 30 signals, consisting of seven quaternary carbons, seven methines, nine methylenes and seven methyls deduced from the DEPT experiments. The most downfield signal resonated at δ180.9 is attributed to the carboxylic acid (C-28). The appearance of signals at δ125.7 and 138.0 indicated the presence of a double bond in urs-12-ene triterpenoid. The combined spectra data analysis using ^{1}H-, ^{13}C-NMR, DEPT, COSY and HSQC shows that UA (**4**) is a pentacyclic triterpene [7-10].



UA (**4**)

Table 1: ^{1}H – NMR and ^{13}C – NMR chemical shifts of UA (4).

Carbon Position	δ ^{13}C (ppm)	DEPT	δ ^{1}H (ppm)
1	38.4	CH_2	
2	28.1	CH_2	
3	78.1	CH	3.43 (1H, br *s*)
4	38.4	C	
5	55.8	CH	
6	18.8	CH_2	
7	33.6	CH_2	
8	40.0	C	
9	48.3	CH	
10	37.4	C	
11	23.6	CH_2	
12	125.6	CH	5.50 (1H, br *s*)
13	139.7	C	
14	42.5	C	
15	28.7	CH_2	
16	24.9	CH_2	
17	48.0	C	
18	53.5	CH	2.52 (1H, *d*, *J* = 11.0 Hz)
19	39.5	CH	
20	39.1	CH	
21	31.1	CH_2	
22	37.3	CH_2	
23	28.8	CH_3	1.24 (*s*)
24	15.7	CH_3	1.02 (*s*)
25	16.6	CH_3	0.93 (*s*)
26	17.4	CH_3	1.05 (*s*)
27	23.8	CH_3	1.22 (*s*)
28	180.0	C	
29	17.5	CH3	0.97 (s)
30	21.4	CH3	0.99 (*d*, 6.1)

1.3 Sources of Ursolic acid

Triterpenoids have been reported in a variety of common European plants and fruits [11-13].

UA (**4**) (3β-hydroxyurs-12-en-28-oic) is a pentacyclic triterpene and a phytosterol. Triterpenes are largely derived from vegetables oils, vegetarian foods, medicinal herbs, cereals, and fruits. They are regarded as natural components of human diets [14]. An estimation of human consumption of triterpenes was approximated to 250mg per day in the developed countries.

It is important to note that in Mediterranean countries, where most of the diets are olive oil based, the average intake of triterpenes consumed by a person could reach 400mg/kg/day [14]. In recent time, there is an unprecedented interest in triterpenes. The bulk of the researches were focused on the cholesterol-lowering properties of triterpenes. The literature is saturated with published data suggesting suitability of

triterpenes in the treatment of wide variety of disease conditions.

UA (**4**) is widely distributed especially in higher plants e.g *Rosmarinus officinalis, Glechoma hederaceae, Ilex paraguariensis, Ichnocarpus frutescens, Phoradendron juniperinum, Syzygium claviflorum, Hyptis capitata* [7], [15-17]. It is a constituent of several herbal medicines marketed in Asia and worldwide for inflammatory conditions [18].

Among berries, North American cranberry fruit (*Vaccinum macrocarpon*), in particular contains a signficant quantity of UA (**4**) in its peel. It is found in the aglycone form and as the *cis* and *trans* p-hydroxyl cinnamate esters [19]. Quantitave analysis of cranberry fruit and products by liquid chromatography-mass spectrometry (LC-MS) found the UA (**4**) content of whole cranberry fruit of different cultivars to range between 60 to 110 mg per 100g of fresh fruit [20]. A similar content is found in sweetened, dried fruit. Considerably less UA (**4**) is determined in jellied cranberry sauce or commercial cranberry juice due presumably to its low solubility in water [21].

Sea buckthorn (*Hippophae rhamnoides* L.) is an industrially cultivated berry in northern Europe. Phytochemical analysis showed that UA (**4**) was much higher in buckthorn berry extract than other berries [22]. Furthermore, Fang and Mc laughlin (1989) have isolated UA (**4**) from red berries of the decorative shrub winterberry (*Ilex verticilata*)[23] . Winterberry is not recommended for human consumption (USDA/NRCS plant fact sheet) [24]. UA (**4**), OA (**5**) and their derivatives have been reported in non-berry fruits including apple (*Malus pumila*). Aglycones and several cinnamoyl and hydoxycinnamoyl esters of UA (**4**) and OA (**5**) were isolated from apple peels [25]. Table 2 presents selected list of medicinal plants containing UA (**4**).

Table 2: Some medicinal plants containing UA (**4**).

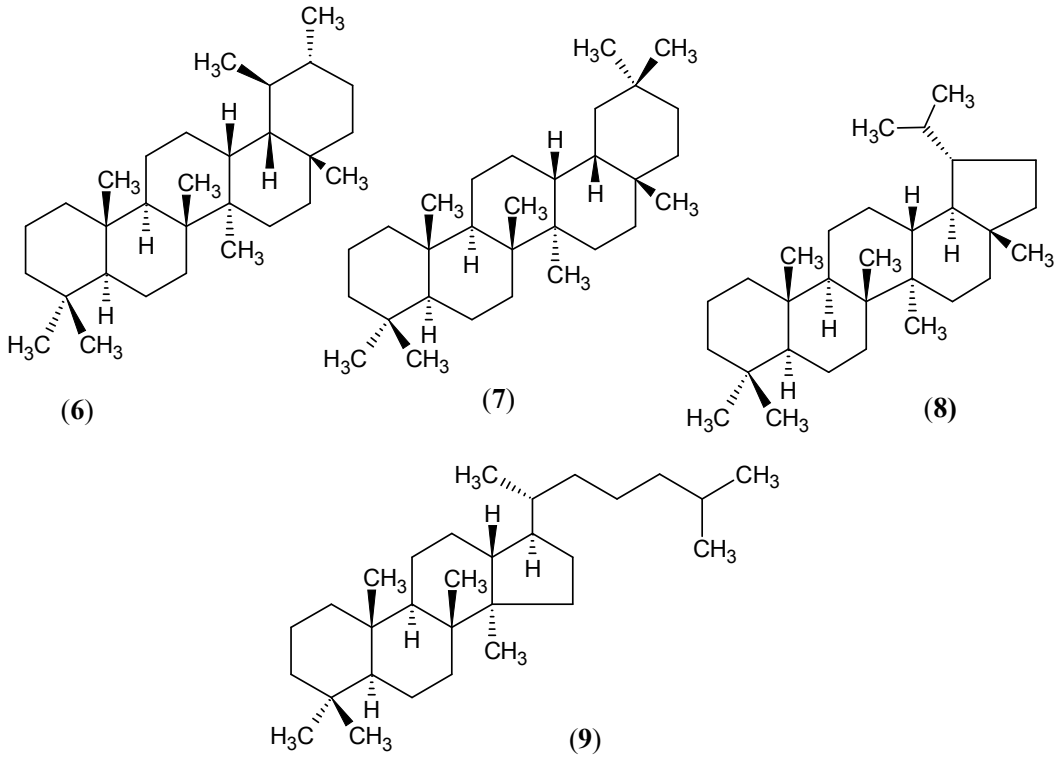
Botanical Name	Common Name	Family
Ocimum sanctum L.	Holy Basil (Tulsi)	Lamiaceae
Vaccinum myrtillus L.	Bilberry	Vacciniaceae
Harpagophytum procumbens DC	Devil's Claw	Pedaliaceae
Sambucus nigra L.	Elder Flowers (European Variety)	Caprifoliaceae
Mentha piperita L.	Peppermint leaves	Lamiaceae
Vinca minor L.	Periwinkle	Apocynaceae
Lavandula augustifolia Mill.	Lavender	Lamiaceae
Origanum vulgare L.	Oregano	Lamiaceae
Thymus vulgaris L.	Thyme	Lamiaceae
Crataegus laevigata (Poir) DC	Hawthorn	Rosaceae
Prunus laurocerasus L.	Cherry laurel leaves	Rosaceae
Arctostaphylos uva-ursi	Bearberry	Ericaceae
Coffea arabica	Coffee	Rubiaceae
Eucalyptus spp.	Eucalyptus	Myrtaceae
Malus domestica	Different apples	Rosaceae
Melissa officinalis	Lemon balm	Lamiaceae
Nerium oleander	Oleander	Apocynaceae
Plantago major	Greater plantain	Plantaginaceae
Rosmarinus officinalis	Sage	Lamiaceae

1.4 Ursolic acid (4) and Pharmacology

UA (**4**) was considered to be pharmacologically inactive for a long time. Thus, UA (**4**) and its alkali salts (e.g. potassium or sodium ursolates) were exclusively used as emulsifying agents in pharmaceutical, cosmetics and food preparation. However, upon closer examination, UA (**4**) was found to be medicinally active both topically and internally [26]. The triterpenoids have a range of unique and potentially usable biological effects and reference to the use of plants with high saponin/triterpenoids content can be found in the first written herbaria. From biological point of view, the most important triterpenoid structures

are ursane (**6**), oleane (**7**), lupane (**8**), and dammarane-euphane (**9**). UA (**4**) has been shown to exhibit various pharmacological activities under in vitro and in vivo conditions.

This ubiquitous pentacyclic triterpene has been studied for its ant-inflammatory, heptoparotective, analgesic, antimicrobial, antimycotic, virostatic, immunomodulatory, diueretic, anti- spasmodic, anti-atherosclerotic, anti-tumor and anti HIV activity [27-34].



1.5 Antimicrobial and Anti-inflammatory activity

Medicinal plants containing UA (**4**) have been used in folk medicine before it was known which constituents were responsible for their therapeutic effectiveness. Contemporary scientific research which led to the isolation and identification of UA (**4**) revealed and confirmed potential anti-microbial and pharmacological activities of the compound, and its derivatives. UA (**4**) has been reported extensively in the literature to posses a wide spectrum of activity including anti-bacterial, anti-fungal and anti-mycotic. The anti-inflammatory activity of pentacyclic triterpenes is well known, and structure –activity relationships have been reviewed [31] . Studies conducted by Racio et al., (1995) and Baricevic et al., (2001) revealed that UA (**4**) reduced inflammation in mouse-ear edema models [32],[33].

The inhibitory effect of UA (**4**) on COX-2 catalysed prostaglandin biosynthesis was observed on proinflammatory pathways has been reported [34].

In a different study, the inhibition of COX-2 transcription in a human mammary oncogenic epithelial cell line (184B5/HER) and observed gene suppression involving protein kinase C signal transduction pathway has been attributed to UA (**4**) [35] .

Recently, cranberry extracts were evaluated for their anti-inflammatory activity, and a methanol – soluble extract was found to inhibit the activity of COX-2 at µ50 g/ml based on measuring conversion of arachidonic acid to prostaglandin

E2 [36]. UA (**4**) has received little attention as a functional food factor, despite its recognition as an anti-inflammatory agent [18].

1.6 Anti-cancer Activity

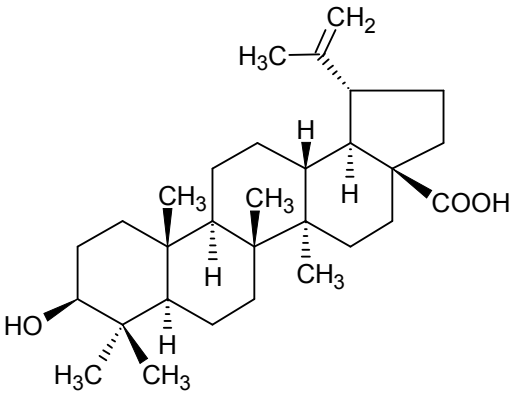
The anti-poliferative activity of UA (**4**) has been reported in a wide variety of cancer cell lines [30]. Ursolic acid hydoxycinnamate esters isolated from cranberry fruit were evaluated for anti-tumor activity in an 60 tumor cell line panel through the National Cancer Institute's Developmental Therapeutics programme (http://dtp.nci.nih.gov/about.html). The esters inhibited the growth of several lung, colon, breast and renal cancers, melanoma and leukemia cell lines with GI_{50} valves based on sulforhodamine B (SRB) assay of between 1.2 and 11 µM [19],[20],[37].

1.7 Anti-Platelet Aggregation

Platelet aggregation inhibition of pentacyclic triterpenes – ursolic, oleanolic, maslinic and mixture of oleanolic and betulinic acids has been investigated in vivo. In the study, the anti-platelet aggregation of UA (**4**) and three other triterpenes was evaluated against thrombin, ADP and epinephrine induced rat platelet aggregation. The triterpenes exhibited a dose dependent inhibitory activity on platelet aggregation induced by the three platelet agonists [38]. In a different study, platelet aggregation inhibition of UA (4) and its semi-synthetic acetyl derivatives have also been reported [39].

1.8 Anti-HIV/AIDS

Anti-HIV activity of UA (4) isolated form *Prosopis glandulosa* (Leguminasae), *Phoradendron juniperinum* (Loranthaceae), S*yzygium claviflorum* (Myrtaceae) and *Hyptis capitata* (Lamiaceae) were evaluated (EC_{50} value of 4.4 µM) and was found to exhibit a level of activity similar to that shown by oleanolic acid (**5**) though somewhat toxic to H_9 cells revealed by the small TI value of 3.3 [40]. Comparative analysis of anti--HIV activity of 3-O- acyl ursolic acid derivatives and its sodium and potassium salts with oleanolic acid (**5**) and betunilic acid (**10**) have been reported [16]. In a different study, the anti –HIV activity of ursolic acid and twelve of its derivatives obtained through structural modifications of positions 2, 3,19 and 27 showed remarkable activity but slightly toxic(EC_{50} = 2.0µg/ml, IC_{50} = 6.5µg/ml (H9 cells), TI = 3.3) [37].



(**10**)

1.9 Anti-Mycobaterium Tuberculosis

The activity of plants derived terpenoids against *Mycobacterium tuberculosis* has appeared in many reviews of antimycobacterial natural products [41-43]. The ubiquitous UA (**4**) has been reported to exhibit growth inhibition of *M. tuberculosis* $H_{37}R_v$ with MIC of 41.9µgl/ml (isolated from the Latin American plant *Valeriana laxiflora*).

An extensive array of triterpenoids has been reported to exhibit antimycobacterial activity. Ursane (**6**) skeleton triterpenes are reported to exhibit mild growth inhibition properties towards *M. tuberculosis* with MIC values of ≥ 15µgml^{-1}. UA (**4**) isolated form *Aspidosperma quebrachoblanco*, exhibited MIC of 15µgml^{-1} [44]. The MIC obtained for UA (**4**) isolated from the Latin America plant *valeriana laxiflora* was 41.9µgml^{-1}. Similarly an MIC of 12.5µgml-1 and 32µm were reported of UA (**4**) obtained from different sources against mycobacterium tuberculosis [41],[45].

In 2008, an interesting dimension was added to the studies on pharmacological activities of Ursolic acid. In the report, Purity-.Activity Relationship (PAR) of different samples of Ursolic acid profiled using quantitative ^{1}H NMR, MICs against two resistant strain of *Mycobacterium tuberculosis* and IC_{50} values in

Vero cells. The profile revealed an inverse correlation of purity and ant-TB bioactivity. The results implies that synergistic effects of Ursolic acid and it`s varying impurity are the likely be the cause of previously reported anti-mycobacterial potential of Ursolic acid [34].

2. Conclusion

This review presents updated reports on the literature of Ursolic acid and some of its natural and semi-synthetic analogs as potential natural products. Considering the numerous pharmacological activities reported of the compound and its ubiquitous nature, there is clear need for further search on the bioavailability of this compound and quantitation in different plant parts and fruits. Further work is also required on the development of synthetic derivatives with lower toxic effect and higher therapeutic potential. Another virgin area is the mechanism of action of the therapeutic effects of this compound; as well as its potentials as functional food factor.

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