

Phytochemical compendium of *Withania somnifera* (Solanaceae): 1965-2014

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ABSTRACT

Withania somnifera Dunal (Solanaceae), commonly known as *ashwagandha*, is the most popular botanical used within the Hindu traditional Ayurvedic system of medicine, where it is predominantly utilized for the treatment of arthritis, anxiety, and stress. Beginning in 1965 with the discovery of withaferin A (**1**), researchers have invested five decades in pursuit of the phytochemical constituents responsible for these activities. Such exhaustive research has resulted in the discovery of 167 natural products, which include a variety of C₂₈ steroids that are commonly known as withanolides (**1-127**). Our in depth analysis of published NMR values revealed inconsistent data related to ten withanolide structures (**58**, **59**, **83**, **85**, **86**, **87**, **93**, **101**, **103** and **126**). Subsequent structural elucidations utilizing these data revealed that withasomnilide (**58**), 6 β ,7 β -epoxy-5 α ,14 α ,17 α -trihydroxy-1-oxo-witha-2,24-dienolide (**59**), 27-acetoxy-5 β -chloro-4 β ,6 α -dihydroxy-1-oxo-witha-2,24-dienolide (**93**), and sominolide (**103**) are more likely withanone (**40**), 20-deoxy-14 α -hydroxy-withanolide Y (**59a**), 27-acetoxy-6 α -chloro-4 β ,5 β -dihydroxy-1-oxo-witha-2,24-dienolide (**93a**), and withaferin A (**1**), respectively. Herein we discuss these discrepancies, and present the first comprehensive review of the species that compiles all phytochemical discoveries made between 1965 and 2014.

KEYWORDS: *Withania somnifera*, withanolide, structure revision, sominolide, withasomnilide,

6 β ,7 β -epoxy-5 α ,14 α ,17 α -trihydroxy-1-oxo-witha-2,24-dienolide, 27-acetoxy-5 β -chloro-4 β ,6 α -dihydroxy-1-oxo-witha-2,24-dienolide, 5 α ,6 α -epoxy-7 α ,14 α ,17 α -trihydroxy-1-oxo-witha-2,24-dienolide, 20-deoxy-14 α -hydroxy-withanolide Y, 27-acetoxy-6 α -chloro-4 β ,5 β -dihydroxy-1-oxo-witha-2,24-dienolide

INTRODUCTION

Withania somnifera (L.) Dunal, referred to as *ashwagandha* in Sanskrit, commonly known in English as either “indian ginseng” or “winter cherry”, is a perennial shrub cultivated in India, parts of East Asia, the Mediterranean region, and North Africa. This plant is the most popular medicinal herb in the Hindu traditional Ayurvedic system of medicine, where for over 3,000 years it has been claimed to be effective against arthritis, anxiety, insomnia and stress. The scientific name of species literally translates as “sleep-inducer” from the Latin *somnifera*. Traditionally the *ashwagandha* (literal translation “horse’s smell”) roots were utilized to create a tonic that increased vitality and longevity. Classified as an adaptogen, this botanical has been used to build sexual energy, calm the mind, promote healthy sleep, reduce nervous exhaustion and relieve weakness [1-2]. Herbal preparations of *W. somnifera* have found wide acceptance in the global market, including the United States, where the powdered roots as well as root extracts are currently available as dietary supplements.

Beginning in the 1960s, researchers from around the world have sought to isolate and identify the

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chemical constituents responsible for the medicinal properties of this species. It is now widely agreed that the major bioactive components from *W. somnifera* are withanolides – a group of C₂₈ steroids characterized by an ergostane skeleton with a C₂₂-hydroxy-C₂₆-oic acid δ -lactone in the nine-carbon side chain [3] (Figure 1). The first fully characterized withanolide structure was completed in 1965 and named withaferin A (**1**) [4] (Figure 2). In subsequent years, an array of extensive phytochemical investigations on different plant parts of this species have resulted in the isolation of more than 120 (**1-127**, Figure 3 and Table 1) structurally diverse withanolides, such as the main components withaferin A (**1**), 27-deoxy-withaferin A (**2**), withanolides A, B, and D (**34**, **38**, and **23**); 27-hydroxy-withanolide A (**35**), 27-hydroxy-withanolide B (**39**), withanone (**40**), 27-hydroxy-withanone (**44**); withanosides IV, VI, and X (**109**, **111**, and **115**) [5-8] (Table 1) (Figures 2 and 3).

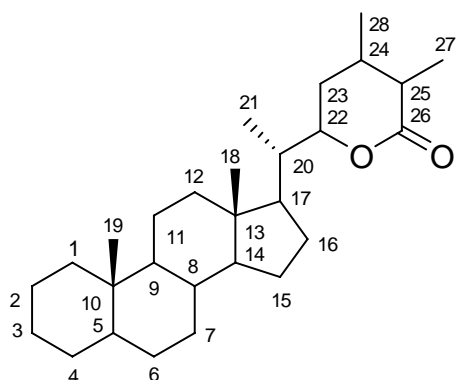


Figure 1. The carbon skeleton of unmodified withanolides.

These withanolides have exhibited potent anti-tumor, anti-stress, and immune-modulatory activities [1, 2]. As typified by withaferin A (**1**), many withanolides have repeatedly shown promising *in vitro* anti-proliferative and *in vivo* anti-tumor properties. Herein, we present the first comprehensive review of *W. somnifera* that summarizes phytochemical advances with an emphasis on withanolide research.

In addition to the withanolides (**1-127**), phytochemical research on *W. somnifera* has resulted in the isolation of an additional 40 secondary metabolites, which includes 19 alkaloids [9-13], four flavonoids [14], three coumarins [15, 16], and five miscellaneous natural products [14, 15, 17].

1. Withanolides in *Withania somnifera*

In 1965, the first structure elucidation of a withanolide resulted in the complete characterization of withaferin A (**1**) [4] and initiated the withanolide chemistry era. The name “withanolide” was originally coined in 1966 [3] to describe this specific type of C₂₈-ergostane steroid, where “withan” refers to the genus “*Withania*” and “olide” represents the δ -lactone in the nine-carbon side chain (Figure 1). The scientific community commonly refers to withanolides that contain the carbon skeleton as shown in Figure 1 as “unmodified withanolides”. Research on plant species outside of the *Withania* genus has resulted in the discovery of hundreds of structural variant withanolides - with changes observed in either the steroid nucleus or side chain - which are collectively referred to as “modified withanolides” [18-21]. The trivial name, withanolide, is still kept and used broadly when referring to either the modified or unmodified variety.

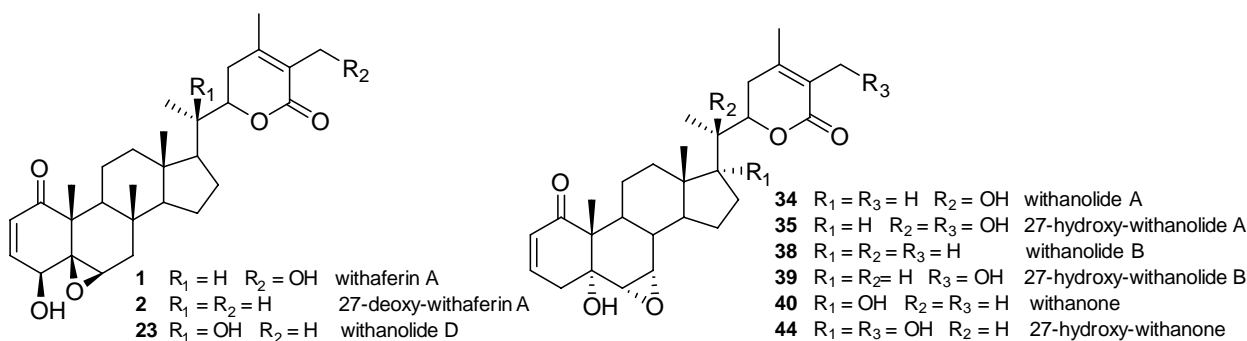
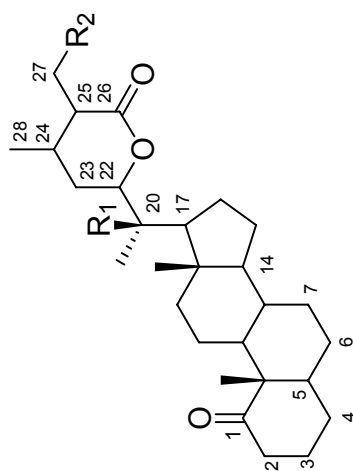


Figure 2. Selected major withanolides in *Withania somnifera*.



No.	Structural features	Common name
1	2,24-dien 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	withaferin A
2	2,24-dien 4 β -OH 5 β ,6 β -epoxy R ₁ = R ₂ = H	27-deoxy-withaferin A
3	2,24-dien 5 β ,6 β -epoxy 7 α -OH 17 α -OH R ₁ = R ₂ = H	14 α -hydroxy-27-deoxy-withaferin A
4	2,24-dien 4 β -OH 5 β ,6 β -epoxy 14 α -OH R ₁ = R ₂ = H	17 α -hydroxy-27-deoxy-withaferin A
5	2,24-dien 4 β -OH 5 β ,6 β -epoxy 17 α -OH R ₁ = R ₂ = H	24,25-dihydro-27-deoxy-withaferin A
6	2-en 4 β -OH 5 β ,6 β -epoxy R ₁ = R ₂ = H	
7	24-en 3 β -OMe 4 β -OH 5 β ,6 β -epoxy R ₁ = R ₂ = H	
8	2,14,24-trien 4 β -OH 5 β ,6 β -epoxy R ₁ = R ₂ = H	14-en-27-deoxy-withaferin A
9	2,16,24-trien 4 β -OH 5 β ,6 β -epoxy R ₁ = R ₂ = H	16-en-27-deoxy-withaferin A
10	2,24-dien 4 β -OH 5 β ,6 β -epoxy 14 α ,15 α -epoxy R ₁ = H R ₂ = OH	14,15-epoxy-withaferin A
11	2,24-dien 4 β -OH 5 β ,6 β -epoxy 17 α -OH R ₁ = H R ₂ = OH	17 α -OH-withaferin A
12	2,24-dien 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OGlc	sitoindoside IX
13	2,24-dien 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = O-(6-O-palmitoyl)-Glc	sitoindoside X
14	24-en 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	2,3-dihydro-withaferin A
15	24-en 3 β -OH 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	viscosalactone B
16	24-en 3 β -OH 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OGlc	
17	24-en 3 β -O-(2-oxo-3,3-dimethyl)cyclopropanyl 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	
18	24-en 3 β -OMe 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	
19	24-en 3 α -(uracil-1-yl) 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	
20	24-en 3 β -(adenin-9-yl) 4 β -OH 5 β ,6 β -epoxy R ₁ = H R ₂ = OH	

Figure 3

21	24-en	3 β -O(CH ₂) ₃ CH ₃	4 β -OH	5 β ,6 β -epoxy	R ₁ = H	R ₂ = OH	withanolide D
22	24-en	3 β -OSO ₃ H	4 β -OH	5 β ,6 β -epoxy	R ₁ = H	R ₂ = OH	14 α -hydroxy-withanolide D
23	2,24-dien	4 β -OH	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H		17 α -hydroxy-withanolide D
24	2,24-dien	4 β -OH	14 α -OH	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H	27-hydroxy-withanolide D
25	2,24-dien	4 β -OH	17 α -OH	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H	24,25-dihydro-withanolide D
26	2,24-dien	4 β -OH	5 β ,6 β -epoxy	R ₁ = R ₂ = OH			4-oxo-withanolide D
27	2-en	4 β -OH	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H		4-oxo-24,25-dihydro-withanolide D
28	2-en	4-oxo	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H		
29	2,24-dien	4-oxo	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H		
30	3 β -OMe	4 β -OH	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H		2,3-dihydro-withanolide D
31	24-en	4 β -OH	5 β ,6 β -epoxy	R ₁ = OH	R ₂ = H		withanolide E
32	2,24-dien	5 β ,6 β -epoxy	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H	17- <i>epi</i> -withanolide E
33	2,24-dien	5 β ,6 β -epoxy	14 α -OH	17 α -OH	R ₁ = OH	R ₂ = H	withanolide A
34	2,24-dien	5 α -OH	6 α ,7 α -epoxy	R ₁ = OH	R ₂ = H		27-hydroxy-withanolide A
35	2,24-dien	5 α -OH	6 α ,7 α -epoxy	R ₁ = R ₂ = OH			24,25-dihydro-withanolide A (ixocarpanolide)
36	2-en	5 α -OH	6 α ,7 α -epoxy	R ₁ = OH	R ₂ = H		2,3-dihydro-3 β -hydroxy-withanolide A
37	24-en	3 β -OH	5 α -OH	6 α ,7 α -epoxy	R ₁ = OH	R ₂ = H	withanolide B
38	2,24-dien	5 α -OH	6 α ,7 α -epoxy	R ₁ = R ₂ = H			27-hydroxy-withanolide B
39	2,24-dien	5 α -OH	6 α ,7 α -epoxy	R ₁ = H	R ₂ = OH		withanone
40	2,24-dien	5 α -OH	6 α ,7 α -epoxy	17 α -OH	R ₁ = R ₂ = H		17- <i>epi</i> -withanone
41	2,24-dien	5 α -OH	6 α ,7 α -epoxy	17 β -OH	R ₁ = R ₂ = H		14 α -hydroxy-withanone
42	2,24-dien	5 α -OH	6 α ,7 α -epoxy	14 α -OH	17 α -OH	R ₁ = R ₂ = H	14 β -hydroxy-withanone
43	2,24-dien	5 α -OH	6 α ,7 α -epoxy	14 β -OH	17 α -OH	R ₁ = R ₂ = H	27-hydroxy-withanone
44	2,24-dien	5 α -OH	6 α ,7 α -epoxy	17 α -OH	R ₁ = H	R ₂ = OH	2,3-dihydro-3 β -hydroxy-withanone
45	24-en	3 β -OH	5 α -OH	6 α ,7 α -epoxy	17 α -OH	R ₁ = R ₂ = H	
46	24-en	3 β -OSO ₃ H	5 α -OH	6 α ,7 α -epoxy	17 α -OH	R ₁ = R ₂ = H	withanolide R
47	2,24-dien	5 α -OH	6 α ,7 α -epoxy	23 β -OH	R ₁ = R ₂ = H		withanolide S
48	2,24-dien	5 α -OH	6 β -OH	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H

Figure 3 continued..

Figure 3

49	2,24-dien	5 α -OEt	6 β -OH	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H	5 α -ethoxy-withanolide S
50	2,24-dien	5 α -OH	6 α ,7 α -epoxy	17 α -OH	R ₁ = OH	R ₂ = H		withanolide T
51	2,17(20),24-trien	5 α -OH	6 α ,7 α -epoxy	16 α -OAc	R ₂ = H			14 α -hydroxy-withanolide R
52	2,24-dien	5 α -OH	6 α ,7 α -epoxy	14 α -OH	17 α -OH	23 β -OH	R ₁ = R ₂ = H	6,7-deoxy-withanolide A (withacogin)
53	2,6,24-trien	5 α -OH	R ₁ = OH	R ₂ = H				6,7-deoxy-withanone
54	2,6,24-trien	5 α -OH	17 α -OH	R ₁ = R ₂ = H				withasomniferol C
55	2,7,24-trien	5 α -OH	14 β -OH	R ₁ = OH	R ₂ = H			withanolide Z
56	2,24-dien	5 α -OH	6 α -OH	7 β -Cl	R ₁ = R ₂ = H			jaborosalactone D
57	2,24-dien	5 α -OH	6 β -OH	R ₁ = H	R ₂ = OH			withasomniide
58	2,24-dien	5 α -OH	6 β ,7 β -epoxy	8 β -OH	R ₁ = R ₂ = H			withanolide Y
59	2,24-dien	5 α -OH	6 β ,7 β -epoxy	14 α -OH	17 α -OH	R ₁ = R ₂ = H		withaoylactone
60	2,24-dien	5 α ,7 α -epoxy	6 α -OH	R ₁ = OH	R ₂ = H			withanolide C
61	2,24-dien	5 α ,6 α -epoxy	7 α -OH	17 α -OH	R ₁ = OH	R ₂ = H		5,6-deoxy-withaferin A
62	2,24-dien	4 β -OH	5 α ,6 α -epoxy	14 α ,15 α -epoxy	R ₁ = H	R ₂ = OH		4-deoxy-5,6-deoxy-withanolide D
63	2,24-dien	5 α -Cl	6 β -OH	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H	withanolide F
64	2,5,24-trien	4 β -OH	R ₁ = H	R ₂ = OH				withanolide G
65	2,5,24-trien	R ₁ = OH	R ₂ = H					withanolide H
66	2,5,24-trien	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H			withanolide I
67	2,5,24-trien	14 α -OH	R ₁ = OH	R ₂ = H				27-hydroxy-withanolide I
68	2,5,24-trien	14 α -OH	R ₁ = R ₂ = OH					withanolide J
69	3,5,24-trien	14 α -OH	R ₁ = OH	R ₂ = H				withanolide K
70	3,5,24-trien	14 α -OH	R ₁ = R ₂ = OH					withanolide L
71	2,5,24-trien	14 α -OH	17 α -OH	R ₁ = OH	R ₂ = H			withanolide M
72	3,5,24-trien	14 α -OH	17 α -OH	R ₁ = OH	R ₂ = H			withanolide N
73	2,5,14,24-tetraen	17 α -OH	R ₁ = OH	R ₂ = H				
74	2,5,24-trien	14 α ,15 α -epoxy	17 α -OH	R ₁ = OH	R ₂ = H			
75	2,5,14,24-tetraen	17 α -OH	R ₁ = H	R ₂ = OH				
76	2,5,14,24-tetraene	R ₁ = OH	R ₂ = H					

Figure 3 continued..

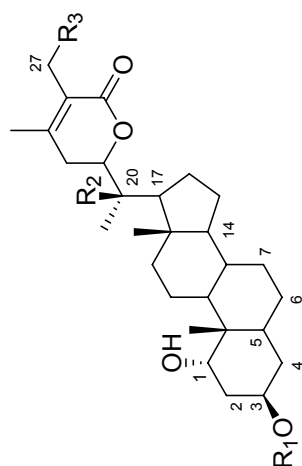
Figure 3

77	2,5,24-trien	4 β -OH	14 α -OH	17 α -OH	R ₁ = R ₂ = H	withanolide O	
78	2,5,24-trien	14 α -OH	17 β -OH	R ₁ = R ₂ = H		withanolide P	
79	2,5,24-trien	17 α -OH	23 β -OH	R ₁ = H	R ₂ = OH	withanolide Q	
80	2,5,24-trien	4 β -OH	14 α -OH	R ₁ = OH	R ₂ = H	withanolide U	
81	2,5,24-trien	7 α -OH	R ₁ = H	R ₂ = OH			
82	2,5,24-trien	17 α -OH	R ₁ = H	R ₂ = OH			
83	2,5,24-trien	R ₁ = OGlc	R ₂ = H			glucosomniferanolide	
84	2,5,16,24-tetraen	14 α -OH	R ₁ = OH	R ₂ = H			
85	2,5,24-trien	8 β -OH	11 β -OH	R ₁ = R ₂ = H		withasomniferanolide	
86	2,5,24-trien	8 β -OH	11 β -OH	16 α ,17 α -epoxy	R ₁ = R ₂ = H	somniferanolide	
87	2,5,24-trien	8 β -OH	18-OH	R ₁ = OH	R ₂ = H	somniferawithanolide	
88	5,24-diene	3 β -OH	R ₁ = OH	R ₂ = H			
89	2,5,24-trien	4 β -OH	7-oxo	17 α -OH	R ₁ = H	R ₂ = OH	
90	24-en	3 α ,6 α -epoxy	4 β -OH	5 β -OH	R ₁ = H	R ₂ = OH	
91	2,24-dien	4 β -OH	5 β -OH	6 α -Cl	R ₁ = OH	R ₂ = H	
92	2,24-dien	4 β -OH	5 β -OH	6 α -Cl	R ₁ = H	R ₂ = OH	
93	2,24-dien	4 β -OH	5 β -Cl	6 α -OH	R ₁ = H	R ₂ = OAc	
94	2,24-dien	4 β -OH	5 β -OH	6 α -Cl	17 α -OH	R ₁ = H	R ₂ = OH
95	2,24-dien	5 β -OH	6 α -Cl	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H
96	2,24-dien	4 β -OH	5 β -OH	6 α -OH	R ₁ = H	R ₂ = OH	
97	24-en	4 β -OH	5 β -OH	6 α -OH	R ₁ = H	R ₂ = OH	
98	2,24-dien	5 β -OH	6 α -OH	14 α -OH	17 β -OH	R ₁ = OH	R ₂ = H
99	2,24-dien	6 α ,7 α -epoxy	23 β -OH	R ₁ = R ₂ = H			
100	2,4,6,24-tetraen	14 α -OH	R ₁ = OH	R ₂ = H			
101	2,4,24-trien	7 β -OH	18-OH	R ₁ = R ₂ = OH		somniwithanolide	
102	4,24-dien	6 α ,7 α -epoxy	17 β -OH	R ₁ = R ₂ = H		withasomniferin A	
103	2,24-dien	4 β -OH	14 α ,15 α -epoxy	R ₁ = H	R ₂ = OH	sominolide	

Figure 3 continued..

Figure 3

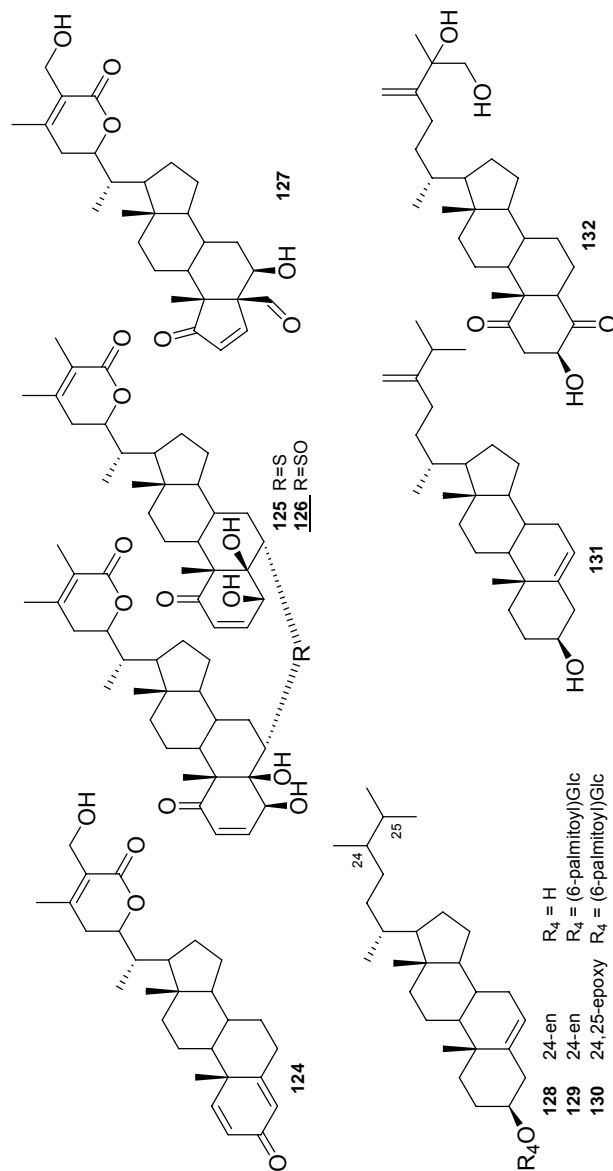
Figure 3 continued..



No.	Structural features	Common name
104	5-en R ₁ = R ₃ = H R ₂ = OH	pubesenolide (sominone)
105	5-en R ₁ = R ₂ = H R ₃ = OH	physagulin D
106	5-en R ₁ = Glc R ₂ = H R ₃ = OH	27-deoxy-physagulin D
107	5-en R ₁ = Glc R ₂ = R ₃ = H	coagulin Q
108	5-en R ₁ = Glc R ₂ = OH R ₃ = H	withanoside IV
109	5-en R ₁ = Glc-(1→6)-Glc R ₂ = H R ₃ = OH	withanoside V
110	5-en R ₁ = Glc-(1→6)-Glc R ₂ = R ₃ = H	withanoside VI
111	5-en R ₁ = Glc-(1→6)-Glc R ₂ = OH R ₃ = H	withanoside VII
112	5-en 7α-OH R ₁ = Glc-(1→6)-Glc R ₂ = R ₃ = H	withanoside VIII
113	5-en R ₁ = Glc-(1→6)-Glc R ₂ = H R ₃ = OGlc	withanoside IX
114	5-en R ₁ = Glc-(1→6)-Glc R ₂ = H R ₃ = OGlc-(1→6)-Glc	withanoside X
115	5-en R ₁ = Glc R ₂ = H R ₃ = OGlc	
116	5-en R ₁ = Glc R ₂ = R ₃ = OH	
117	5-en R ₁ = Glc-(1→6)-Glc-(1→4)-Glc R ₂ = H R ₃ = OH	
118	5-en 24,25-dihydro R ₁ = Glc-(1→6)-Glc R ₂ = OH R ₃ = H	
119	5α-OH 6α,7α-epoxy R ₁ = R ₂ = R ₃ = H	withanoside I
120	5α-OH 6α,7α-epoxy R ₁ = Glc R ₂ = R ₃ = H	withanoside II
121	5α-OH 6α,7α-epoxy R ₁ = Glc-(1→6)-Glc R ₂ = R ₃ = H	withanoside III
122	5α-OH 6α,7α-epoxy R ₁ = Glc R ₂ = H R ₃ = OH	
123	4β-OH 5β,6β-epoxy 16β-OH R ₁ = Glc R ₂ = H R ₃ = OH	

Figure 3

Figure 3 continued..

**Figure 3.** Withanolides (**1-127**) and withanolide precursors (**128-132**) reported from *W. somnifera* (inconclusive withanolide structures are underlined).**Table 1.** Withanolides (**1-127**)[#] from *Withania somnifera*.

No.	Name	Plant part	NMR spectroscopic and X-ray data	Selected bioactivity and note
1	withaferin A (5 β ,6 β -epoxy- β ,27-dihydroxy-1-oxo-witha-2,24-dienolide)	leaves [4], whole plant [81], aerial parts [43], roots [53], leaves [83]	¹ H [4], ¹³ C [82], X-ray [22, 23] ¹ H [83] ¹ H [84]	cytotoxicity [72, 110-115], anti-tumor [116-118], cox-1 inhibitory [54]
2	27-deoxy-withaferin A	leaves [83]		
3	5 β ,6 β -epoxy-7 α ,17 α -dihydroxy-1-oxo-witha-2,24-dienolide	seeds [84]		
4	14 α -hydroxy-27-deoxy-withaferin A	leaves [85]	¹ H [85]	
5	17 α -hydroxy-27-deoxy-withaferin A	leaves [59, 90]	¹ H [59], ¹³ C [80]	pseudonym "tubocapsanolide F" [80]
6	24,25-dihydro-27-deoxy-withaferin A	leaves [54, 83]	¹ H [83]	
7	2,3-dihydro-3 β -methoxy-27-deoxy-withaferin A	whole plant [47]	¹ H and ¹³ C [47, 86]	artifact, pseudonym "quresimine B" [47]

Table 1 continued..

8	14-en-27-deoxy-withaferin A	leaves [59], whole plant [81]	¹ H [59]	
9	16-en-27-deoxy-withaferin A	leaves [7, 34]	¹ H and ¹³ C [34]	
10	14 α ,15 α -epoxy-withaferin A	aerial parts [44]	¹ H and ¹³ C [44]	
11	17 α -hydroxy-withaferin A	whole plant [81], leaves [34]	¹ H and ¹³ C [81]	
12	sitindosides IX	roots [87], aerial parts [43], leaves [54]	¹ H and ¹³ C [88]	
13	sitindosides X	roots [87]	no NMR data	
14	2,3-dihydro-withaferin A	aerial parts [43], roots [54], leaves [6]	¹ H [4], ¹³ C [82]	
15	viscosalactone B	aerial parts [33], leaves [54], root [95]	¹ H and ¹³ C [76]	
16	27-O-glucopyranosyl-viscosalactone B	leaves [54]	¹ H and ¹³ C [54]	
17	3 β -O-(2-oxo-3,3-dimethyl)-cyclopropanyl-2,3-dihydro-withaferin A	leaves [54]	¹ H and ¹³ C [54]	
18	2,3-dihydro-3 β -methoxy-withaferin A	leaves [4], whole plant [47], aerial parts [43]	¹ H [4, 47] and ¹³ C [47, 82]	artifact, pseudonym "quresimine A" [47]
19	2,3-dihydro-3 α -(uracil-1-yl)-withaferin A	leaves and twigs [46]	¹ H and ¹³ C [46]	
20	2,3-dihydro-3 β -(adenine-9-yl)-withaferin A	leaves and twigs [46]	¹ H and ¹³ C [46]	
21	2,3-dihydro-3 β -O-butyl-withaferin A	leaves and twigs [46]	¹ H and ¹³ C [46]	artifact [46]
22	2,3-dihydro-3 β -O-sulfonyl-withaferin A	Aerial parts [33, 46]	¹ H and ¹³ C [33]	
23	withanolide D	leaves [89], aerial parts [43], root [90]	¹ H [89], ¹³ C [62, 120], X-ray [24]	cytotoxicity [72, 112, 119, 120]
24	14 α -hydroxy-withanolide D	leaves [91]	¹ H [91]	
25	17 α -hydroxy-withanolide D	leaves [91]	¹ H [91]	
26	27-hydroxy-withanolide D	leaves [91], aerial parts [43]	¹ H [91]	
27	24,25-dihydro-withanolide D	leaves [83, 92], aerial parts [43]	¹ H [83]	
28	4-dehydro-withanolide D	leaves [92]	¹ H [92]	
29	4-dehydro-24,25-dihydro-withanolide D	leaves [92]	¹ H [92]	
30	3 β -methoxy-2,3,24,25-tetrahydro-withanolide D	aerial parts [43]	¹ H and ¹³ C [43]	artifact [43]
31	2,3-dihydro-withanolide D	leaves [92]	¹ H [92]	
32	withanolide E (5 β ,6 β -epoxy-14 α ,17 β ,20-trihydroxy-1-oxo-witha-2,24-dienolide)	leaves [26, 93]	¹ H [93], ¹³ C [62], X-ray [26]	cytotoxicity [112, 121, 122]
33	17- <i>epi</i> -withanolide E	leaves [32, 94]	¹³ C [62]	
34	withanolide A	roots [16], Leaves [56]	¹ H [16, 56, 68], ¹³ C [62, 68]	synonym "lycium-A" [78]
35	withasomniferol A (27-hydroxy-withanolide A)	roots [16, 95], berries [57]	¹ H [16]	

Table 1 continued..

36	ixocarpanolide (24,25-dihydro-withanolide A)	roots [16], leaves [34], aerial parts [43]	¹ H [16, 77], ¹³ C [34, 77]	pseudonym “withasomiferol B” [16]
37	2,3-dihydro-3 β -hydroxy-withanolide A	whole plant [81]	¹ H and ¹³ C [81]	
38	withanolide B	leaves [55], whole plant [47], roots [16]	¹ H [16, 47, 55, 68], ¹³ C [47, 68, 79, 102], X-ray [24]	synonym “lycium-B” [78], pseudonym “withalactone” [47]
39	27-hydroxy-withanolide B	leaves [40, 59], roots [116]	¹ H [16, 87, 71, 124], ¹³ C [116, 71, 123], X-ray [28]	
40	withanone (17 α -hydroxy-withanolide B)	leaves [59], berries [57]	¹ H [59], ¹³ C [62, 69], X-ray [29]	
41	17- <i>epi</i> -withanone	berries [57]	¹ H and ¹³ C [51, 57]	pseudonym “ <i>iso</i> -withanone” [51]
42	14 α -hydroxy-withanone	leaves [69]	¹ H and ¹³ C [69]	
43	14 β -hydroxy-withanone	leaves [30]	¹ H and ¹³ C [69], X-ray [30]	
44	27-hydroxy-withanone	leaves [34]	¹ H and ¹³ C [34]	
45	2,3-dihydro-3 β -hydroxy-withanone	leaves [34]	¹ H and ¹³ C [34]	
46	2,3-dihydro-3 β - <i>O</i> -sulfonyl-withanone	leaves [34]	¹ H and ¹³ C [34]	
47	withanolide R (23 β -hydroxy-withanolide B)	leaves [96]	¹ H [96]	
48	withanolide S	leaves [93]	¹ H [93], ¹³ C [62]	
49	5 α -ethoxy-withanolide S	leaves [97]	¹ H [97], ¹³ C [94, 97]	
50	withanolide T (17 α -hydroxy-withanolide A)	leaves [27, 56]	¹ H [27, 56], ¹³ C [62]	
51	16 β -acetoxyl-17(20)-ene-withanolide B	roots [95], leaves [17]	¹ H and ¹³ C [95, 102]	
52	14 α ,17 α -dihydroxy-withanolide R	fruits [15]	¹ H and ¹³ C [15]	
53	withacogin (6,7-deoxy-withanolide A)	roots [6]	¹ H and ¹³ C [68]	
54	6,7-deoxy-withanone	leaves [59]	¹ H [59], ¹³ C [62]	
55	withasomiferol C	roots [16]	¹ H and ¹³ C [16]	
56	withanoid Z (6 α -chloro-7 β -hydroxy-withanolide B)	leaves [40]	¹ H and ¹³ C [40]	
57	jaborosalactone D	leaves and twigs [46]	¹ H [98], ¹³ C [99]	
58	withasomilide	stem barks [67]	¹ H and ¹³ C [67]	
59	6 β ,7 β -epoxy-5 α ,14 α ,17 α -trihydroxy-witha-2,24-dienolide	leaves [69]	¹ H [69]	suggested to be withanone 40
60	5 α ,7 α -epoxy-6 α ,20-dihydroxy-1-oxo-witha-2,24-dienolide	roots [95]	¹ H and ¹³ C [95]	suggested to be 20-deoxy-14 α -hydroxy-withanolide Y
61	withanolide Y	leaves [27]	¹ H and X-ray [27]	
62	withaoxylactone	whole plant [47, 56]	¹ H and ¹³ C [47, 56]	

Table 1 continued..

63	withanolide C	leaves [41]	¹ H and ¹³ C [41]	cytotoxicity [72]
64	5,6-deoxy-withaferin A	leaves and twigs [46], root [24]	¹ H and ¹³ C [100], X-ray [24]	
65	4-deoxy-5,6-deoxy-withanolide D	whole plant [101]	¹ H and ¹³ C [75, 101]	
66	Withanolide F	leaves [26, 93]	¹ H [70, 93], ¹³ C [70]	
67	withanolide G	leaves [32, 61]	¹ H [61], ¹³ C [62]	
68	withanolide H	leaves [32, 61]	¹ H [61], ¹³ C [62]	
69	withanolide I	leaves [32, 61]	¹ H [61], ¹³ C [62]	
70	27-hydroxy-withanolide I	leaves [97]	¹ H [97], ¹³ C [62]	
71	withanolide J	leaves [32, 61]	¹ H [61, 70], ¹³ C [62, 70]	
72	withanolide K	leaves [32, 61]	¹ H [61], ¹³ C [62]	
73	withanolide L	leaves [61]	¹ H [61]	
74	withanolide M	leaves [61]	¹ H [61]	
75	withanolide N	leaves [91]	¹ H [91]	
76	17-deoxy-withanolide L	leaves [45]	¹ H [61]	
77	withanolide O	leaves [91]	¹ H [91]	
78	withanolide P	leaves [91, 93]	¹ H [91, 93], ¹³ C [62]	
79	withanolide Q	leaves [96]	¹ H [96]	
80	withanolide U	leaves [32, 56]	¹ H [56], ¹³ C [62]	
81	4-deoxy-5,6-deoxy-7 α -hydroxy-withaferin A	leaves [59]	¹ H [59], ¹³ C [124]	
82	4-deoxy-5,6-deoxy-17 α -hydroxy-withaferin A	leaves [59]	¹ H [59]	
83	glucosomiferanolide	roots [74]	¹ H and ¹³ C [74]	inconclusive structure
84	14 α ,20-dihydroxy-witha-2,5,16,24-tetraenolide	leaves [103]	¹ H and ¹³ C [103]	
85	withasomiferanolide	stem barks [67]	¹ H and ¹³ C [67]	inconclusive structure
86	sommiferanolide	stem barks [67]	¹ H and ¹³ C [67]	inconclusive structure
87	sommiferawithanolide	stem barks [67]	¹ H and ¹³ C [67]	inconclusive structure
88	3 β ,20-hydroxy-1-oxo-witha-5,24-dienolide	leaves [97]	¹ H [97]	
89	4 β ,17 α ,27-trihydroxy-1,7-oxo-witha-2,5,24-trienolide	leaves [7]	¹ H and ¹³ C [7]	
90	3 α ,6 α -epoxy-4 β ,5 β ,5 β ,27-trihydroxy-1-oxo-witha-24-enolide	roots [6]	¹ H and ¹³ C [6]	more likely artifact
91	6 α -chloro-5 β -hydroxy-withanolide D	leaves [42]	¹ H and ¹³ C [42]	
92	6 α -chloro-5 β -hydroxy-withaferin A	aerial part [43], leaves [25]	¹ H and ¹³ C [25, 42]	

Table 1 continued..

93	5 β -chloro-6 α -hydroxy-27-acetyl-withaferin A	aerial parts [44]	¹ H and ¹³ C [44]	inconclusive structure
94	6 α -chloro-5 β ,17 α -dihydroxy-withaferin A	leaves [25]	¹ H, ¹³ C, and X-ray [25]	
95	6 α -chloro-5 β -hydroxy-withanolide E	leaves [42, 45]	¹ H and ¹³ C [42, 104], X-ray [42]	synonym "4-deoxy-physalolactone" [104]
96	2,3-didehydro-sommifericin	whole plant [56], aerial part [43], leaves [25], root [6]	¹ H and ¹³ C [43, 56]	synonym "5 β ,6 α -dihydroxy-withaferin A" [43]
97	sommifericin	whole plant [56]	¹ H and ¹³ C [56]	
98	5 β ,6 α -dihydroxy-withatholide E	fruits [15]	¹ H and ¹³ C [15]	
99	5-deoxy-withanolide R	whole plant [105]	¹ H [105]	
100	14 α ,20-dihydroxy-1-oxo-witha-2,4,6,24-tetraenolide	leaves [69]	¹ H [69]	
101	somniwithanolide	stem barks [67]	¹ H and ¹³ C [67]	inconclusive structure
102	withasomiferin A	whole plant [105]	¹ H [105]	
103	sominolide	whole plant [52]	¹ H [52]	suggested to be withaferin A (1)
104	1 α ,3 β ,20-trihydroxy-witha-5,24-dienolide	leaves [97], aerial parts [43]	¹ H and ¹³ C [97], X-ray [31]	
105	pubesenolide	whole plant [52], aerial parts [43, 46]	¹ H and ¹³ C [52, 58]	pseudonym "sominone" [52]
106	physagulin D	aerial parts [43], roots [53], leaves [6]	¹ H and ¹³ C [106]	
107	27-deoxy-physagulin D	leaves [107]	¹³ C ^s	
108	coagulin Q	roots [53]	¹ H and ¹³ C [108]	
109	withanoside IV	roots [53], fruits [12], leaves [6]	¹ H and ¹³ C [53]	
110	3-O-[β -D-glucopyranosyl (1 \rightarrow 6)- β -D-glucopyranosyl]-1 α ,3 β -dihydroxy-witha-5,24-dienolide	aerial parts [43], roots [53], fruits [12]	¹ H and ¹³ C [43, 53]	pseudonym "withanoside V" [53]
111	withanoside VI	roots [53], fruits [12]	¹ H and ¹³ C [53]	
112	withanoside VII	roots [53]	¹ H and ¹³ C [53]	
113	withanoside VIII	roots [6]	¹ H and ¹³ C [6]	
114	withanoside IX	roots [6]	¹ H and ¹³ C [6]	
115	withanoside X	roots [6], leaves [54]	¹ H and ¹³ C [6, 54]	pseudonym "27-O- β -D-glucopyranosyl-physagulin D" [54]
116	withanoside XI	roots [6]	¹ H and ¹³ C [6]	
117	3 β -O-Glc-(1-6)Glc-(1-4)Glc-pubesenolide	leaves [54]	¹ H and ¹³ C [54]	
118	24,25-dihydro-withanoside VI	fruits [12]	¹ H and ¹³ C [12]	
119	6 α ,7 α -epoxy-1 α ,3 β ,5 α -trihydroxy-witha-24-enolide	leaves [59], berries [57]	¹ H [51, 59], ¹³ C [51]	

Table 1 continued..

120	withanoside I	roots [53]	¹ H and ¹³ C [53]
121	withanoside II	roots [53]	¹ H and ¹³ C [53]
122	withanoside III	roots [53]	¹ H and ¹³ C [53]
123	5β,6β-epoxy-4β,16β-dihydroxy-physagulin D	leaves [53]	¹ H and ¹³ C [53]
124	withasomidenone	leaves [34], whole plant [60]	¹ H and ¹³ C [34, 60]
125	ashwagandhanolide	roots [35]	¹ H and ¹³ C [35]
126	oxygenated ashwagandhanolide	roots [36]	¹ H and ¹³ C [36]
127	5β-formyl-6β,27-dihydroxy-1-oxo-4-nor-witha-24-enolide	leaves [25]	¹ H [4, 49], ¹³ C [109]*

*Inconclusive withanolide structures are underlined.

§The ¹³C NMR data (ppm measured in C₃D₅N) of withanolide **107** (27-deoxy-physagulin D) were generously provided by Prof. Junei Kinjo (Fukuoka University, Fukuoka, Japan) as follows: C₁ 72.3, C₂ 37.8, C₃ 73.9, C₄ 39.1, C₅ 139.2, C₆ 124.0, C₇ 32.2, C₈ 32.1, C₉ 41.5, C₁₀ 42.1, C₁₁ 20.5, C₁₂ 39.6, C₁₃ 42.8, C₁₄ 56.4, C₁₅ 24.6, C₁₆ 27.3, C₁₇ 52.1, C₁₈ 11.7, C₁₉ 19.6, C₂₀ 39.3, C₂₁ 13.4, C₂₂ 78.6, C₂₃ 29.6, C₂₄ 149.7, C₂₅ 121.9, C₂₆ 166.6, C₂₇ 12.7, C₂₈ 20.1, C_{1'} 102.7, C_{2'} 75.2, C_{3'} 78.4, C_{4'} 71.4, C_{5'} 78.3, C_{6'} 62.5.

¶The ¹³C NMR data (ppm measured in CDCl₃) of withanolide **127** are: C₁ 216.3, C₂ 31.0, C₃ 31.4, C₄ 204.2, C₅ 60.4, C₆ 67.4, C₇ 32.2, C₈ 32.1, C₉ 41.8, C₁₀ 52.3, C₁₁ 21.1, C₁₂ 39.0, C₁₃ 42.6, C₁₄ 55.9, C₁₅ 23.9, C₁₆ 27.0, C₁₇ 51.6, C₁₈ 12.0, C₁₉ 13.2, C₂₀ 38.7, C₂₁ 13.4, C₂₂ 78.8, C₂₃ 29.1, C₂₄ 152.7, C₂₅ 126.0, C₂₆ 167.0, C₂₇ 57.5, C₂₈ 20.0 [109].

Synonym 27-hydroxy-3-oxo-witha-1,4,24-trienolide [34]

inconclusive structure

Withania somnifera is the first species to afford such unmodified withanolides, where many have been given trivial names such as withanolides A-U (**34**, **38**, **63**, **23**, **32**, **66-69**, **71-75**, **77-79**, **47**, **48**, **50**, and **80**), Y (**61**) and Z (**56**); and a series of saponins which include sitoindosides IX, X (**12**, **13**), 27-*O*-glucopyranosyl-viscosalactone B (**16**), withanosides I-XI (**120-122**, **109-116**), physagulin D (**106**), 27-deoxy-physagulin D (**107**), and coagulin Q (**108**) (Figure 3 and Table 1). X-ray crystallography experiments have confirmed the structures of withaferin A (**1**) [22, 23], 5,6-deoxy-withaferin A (**64**) [24], 6 α -chloro-5 β ,17 α -dihydroxy-withaferin A (**94**) [25], withanoides B, D, E, and Y (**38**, **23**, **32**, and **61**) [24, 26, 27], 27-hydroxy-withanolide B (**39**) [28], withanone (**40**) [29], 14 β -hydroxy-withanone (**43**) [30], and 1 α ,3 β ,20-trihydroxy-witha-5,24-dienolide (**104**) [31]. Compounds **1-127** represent the largest number of withanolides isolated from any single species to-date.

All withanolides isolated from *W. somnifera* exhibited C₁, C₂₂ as well as C₂₆ oxygenation patterns, while some isolates presented additional oxygenation at C-3, 4, 5, 6, 7, 14, 17, 20, 23, and 27 (Figure 3). For the convenience of presentation, these highly-oxygenated chemical species are grouped according to specific structural characteristics such as the presence of a 5 β ,6 β -epoxy (**1-33**, **123**), 5 α -hydroxy (**34-62**, **119-122**), 5 α -chlorine (**63**), 5-en (**64-89**, **104-118**), or 5 β -hydroxy (**90-98**, **125**, **126**) functionality.

Variations have also been found within the nine-carbon side chain at C-17, which could be in either α or β orientation. This is exemplified by a pair of isomers, withanolide E (**32**) [26] and 17-*epi*-withanolide E (**33**) [32], reported simultaneously in the plant.

The majority of isolated withanolides contain just carbon, hydrogen and oxygen in their structures, however, there are reports which show the presence of sulfurated (Section 1.1) and chlorinated (Section 1.2) withanolides which are not commonly encountered in natural steroids.

1.1. Sulfurated withanolides

Sulfur-containing withanolides are rarely observed in nature. A combined total of four sulfurated withanolides have been reported in this

species. They include 2,3-dihydro-3 β -*O*-sulfonyl-withaferin A (**22**) [33], 2,3-dihydro-3 β -*O*-sulfonyl-withanone (**46**) [34] as well as two dimers: ashwagandhanolide (**125**) [35] and oxygenated ashwagandhanolide (**126**) [36]. In addition, it was recently reported that **22** is the precursor of withaferin A (**1**) as it can spontaneously be converted into **1** by an elimination reaction [33]. This suggests that compound **46** is likely the precursor of withanone (**40**), which is another main component present in the plant.

1.2. Withanolide precursors

Several phytochemical studies of *ashwagandha* resulted in the isolation of five withanolide precursors: 3 β -hydroxy-5,24(25)-dien-ergostane (**128**) [37], sitoindosides VII and VIII (**129**, **130**) [38], 3 β -hydroxy-ergosta-5,24(28)-diene (**131**) [37], and 3 β ,25,26-trihydroxy-1,4-dioxo-ergosta-24(28)-ene (**132**) [17]. It was reported that compound **131** is an important intermediate in the withanolide biosynthesis [39].

1.3. Chlorinated withanolides

Halogenated natural products are not widely spread in terrestrial plants, and chlorinated withanolides are seldom encountered in Solanaceae species. The seven chlorinated withanolides reported from *W. somnifera* are withanolide Z (7 β -chloro-5 α -hydroxy-withanolide B) (**56**) [40], withanolide C (5 α -chloro-6 β -hydroxy-withanolide E) (**63**) [41], 6 α -chloro-5 β -hydroxy-withanolide D (**91**) [42], 6 α -chloro-5 β -hydroxy-withaferin A (**92**) [25, 43], 27-acetoxy-5 β -chloro-6 α -hydroxy-withaferin A (**93**) [44], 6 α -chloro-5 β ,17 α -dihydroxy-withaferin A (**94**) [25], and 6 α -chloro-5 β -hydroxy-withanolide E (**95**) [42, 45]. However, these chlorinated withanolides could be generated during the extraction and purification process from the major withanolides containing epoxide moieties such as withaferin A (**1**), withanolides B, D, and E (**38**, **23**, and **32**) and 17 α -hydroxy-withaferin A (**11**). The epoxide rings in these compounds (either a 5 β , 6 β -epoxy, or 6 α 7 α -epoxy functionality) are vulnerable and easily opened in the presence of HCl [4]. Therefore it is highly likely that the six chlorinated withanolides (**56**, **63**, **91**, **92**, **94**, and **95**) are artifactual products derived from **38**, **32**, **23**, **1**, **11**, and **32**, respectively (Figure 4).

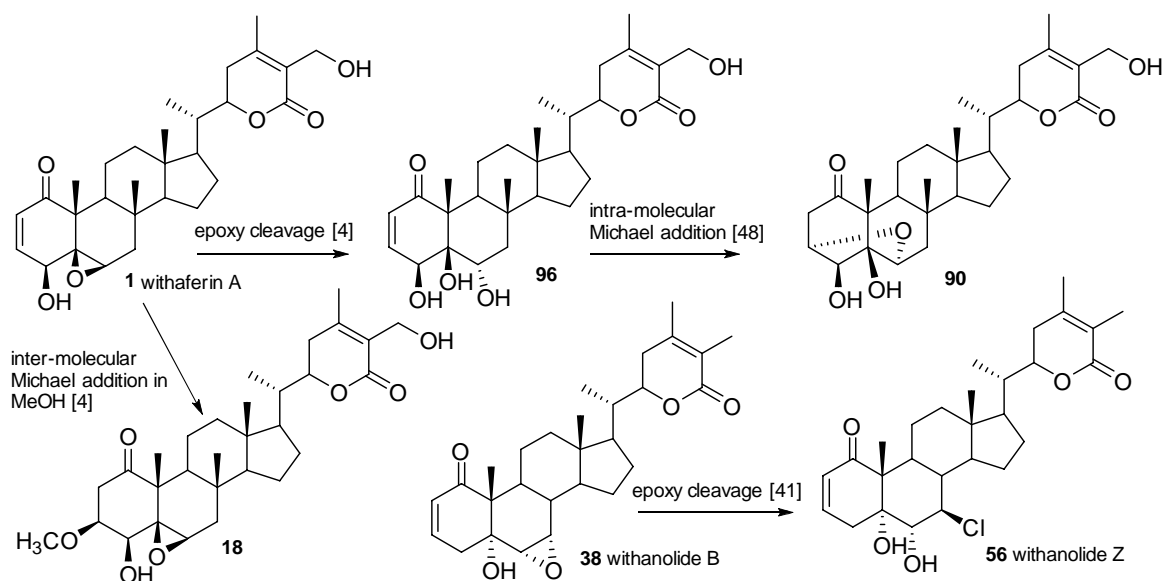


Figure 4. Examples of artifactual withanolides formed by Michael addition or epoxy cleavage.

1.4. Artifactual withanolides

As early as the 1960s, it was observed that in the presence of methanol, the conjugated 1-oxo-2-ene functionality in the ring A of withaferin A (**1**) was susceptible to inter-molecular Michael addition to form artifactual products, such as 2,3-dihydro-3 β -methoxy-withaferin A (**18**) [4] (Figure 4).

Additional examples of decomposition include the formation of 2,3-dihydro-3 β -butoxy-withaferin A (**21**) [46], 2,3-dihydro-3 β -methoxy-27-deoxy-withaferin A (**7**) [47], and 2,3-dihydro-3 β -methoxy-withanolide D (**30**) [43], which are derived from withaferin A (**1**), 27-deoxy-withaferin A (**2**), and 24,25-dihydro-withanolide D (**27**), respectively (Table 1). Furthermore, this α,β -unsaturated carbonyl structural unit could be readily converted by intra-molecular Michael addition to form other artifactual products [21, 48]. For example, 3 $\alpha,6\alpha$ -epoxy-4 $\beta,5\beta,27$ -trihydroxy-1-oxo-witha-24-enolide (**90**) [6] (Table 1) is most likely the artifactual derivative of 5 $\beta,6\alpha$ -dihydroxy-withaferin A (**96**) [48] (Figure 4).

The only modified withanolide 5 β -formyl-6 $\beta,27$ -dihydroxy-1-oxo-4-*nor*-witha-24-enolide (**127**) isolated from *W. somnifera* [25] is more than likely an artifact derived from withaferin A (**1**), since it was reported that the acid-catalyzed pinacol-type rearrangement of **1** led to the formation of **127** [49].

2. Alkaloids in *Withania somnifera*

Although alkaloids are a major group of bioactive natural products in members of the Solanaceae, there is scant information available about the presence of this class of compounds in *W. somnifera*. In contrast to the large number of withanolides isolated, only 19 alkaloids (**137-155**) have been reported from this species during the past 50 years, namely withasomnine (**137**) [9], nicotine (**138**) [10], *iso*-pelletierine (**139**), tropine (**140**), *pseudo*-tropine (**141**), 3 β -tigloxy-tropine (**142**), anhygrine (**143**), anahygrine (**144**), cuscohygrine (**145**), choline (**146**) [11], and withanamides A-I (**147-155**) [12] (Figure 5).

In the early 1950s, several alkaloids were reported and given common names although they were never chemically characterized. These include somniferine in conjunction with somniferinine, somnine, withanine, *pseudo*-withanine, withananine, and withananinine [10, 13]. In an unrelated 1980s study, a dimeric morphine-type alkaloid isolated from the opium poppy (*Papaver somniferum*) was also named as somniferine [50] although its structure does not bear any resemblance to the alkaloid isolated from *W. somnifera*. In view of the advanced techniques and equipment currently available to natural product chemistry researchers, it would be of interest to conduct a more thorough

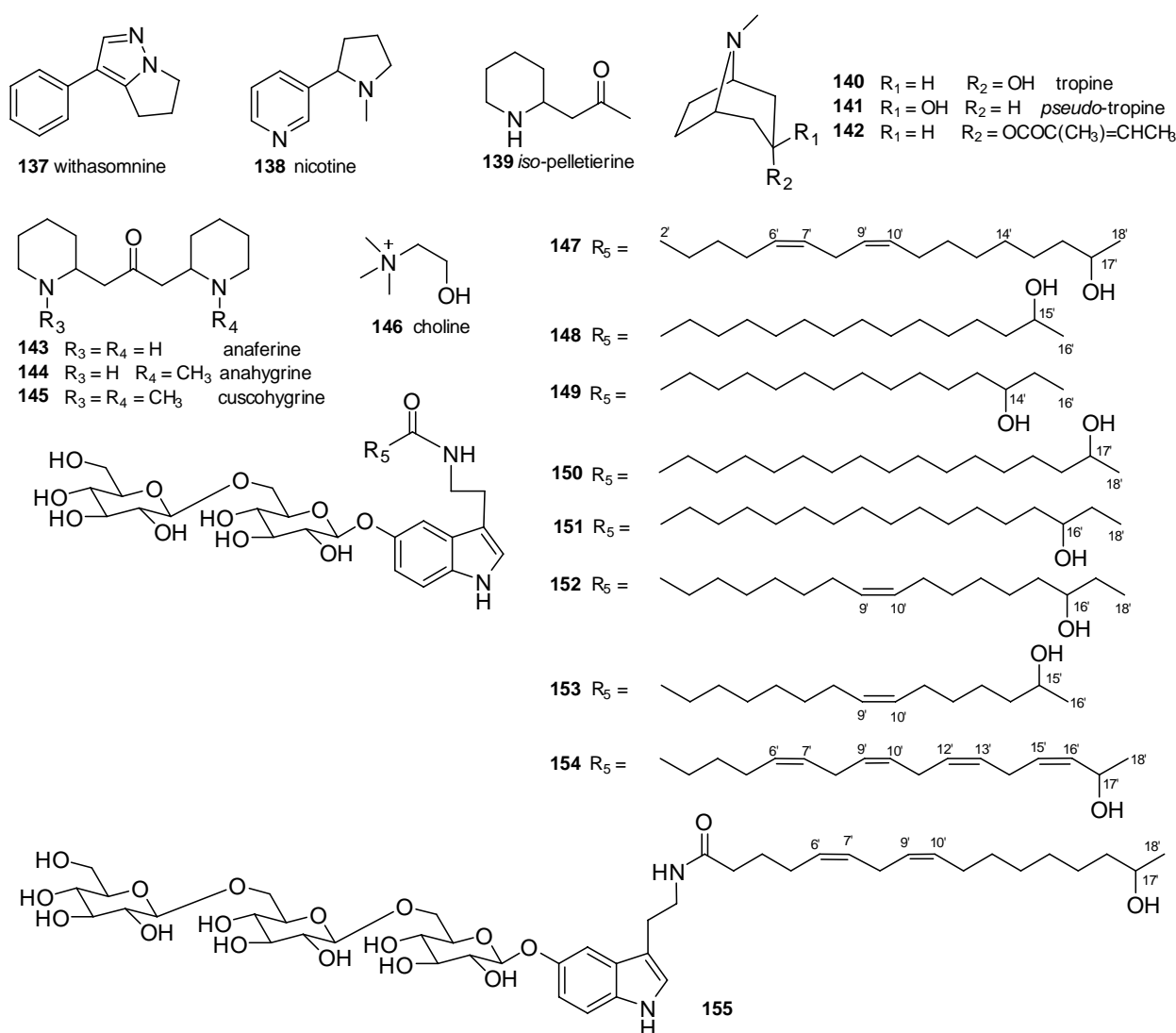


Figure 5. Alkaloids (**137-155**) reported from *W. somnifera*.

search for alkaloids in this medicinal plant and clarify such discrepancies.

3. Other components in *Withania somnifera*

Other natural products isolated from the species include compounds that are broadly distributed throughout the plant kingdom such as commonly occurring phytosterols: β -sitosterol (**133**), 3β -*O*- β -D-glucopyranosyl-sitosterol (**134**), stigmasterol (**135**), 3β -*O*- β -D-glucopyranosyl-stigmasterol (**136**) [15, 16]; common flavonoids: quercetin (**156**) [14], rutin (**157**), 7-*O*- β -D-glucopyranosyl-rutin (**158**) [14], 3-*O*-rutinosyl-6,8-dihydroxy-kaempferol (**159**) [14]; quinic acid (**160**) and its derivatives 4-*O*-

caffeoyl-quinic acid (**161**), 4,5-*O*-dicaffeoyl-quinic acid (**162**) [14]; coumarins: aesculetin (6,7-dihydroxy-coumarin) (**163**) and scopoletin (7-hydroxy-6-methoxy-coumarin) (**164**) [15]; benzo[6:7]chroman (**165**) [16], triterpene β -amyirin (**166**) [15], and 2,5-dioxo-3-tetratriacont-3'-enyl-1,4-dioxane (**167**) [17].

4. Nomenclature discrepancies and suggested structural revisions

Numerous withanolide structures originally reported as “new” at the time of publication were actually already known in the literature, such as quresimine A [47], withasomniferol B [16], withalactone [16, 47],

5 β ,6 α -dihydroxy-withaferin A [43], *iso*-withanone [51], sominone [52], withanoside V [53], 27-*O*- β -D-glucopyranosyl-physagulin D [54], the aglycone of withanoside I [51], and 27-hydroxy-3-oxo-witha-1,4,24-trienolide [34]. These compounds are in fact the known 2,3-dihydro-3 β -methoxy-withaferin A (**18**) [4], ixocarpanolide (**36**) [43], withanolide B (**38**) [55], 2,3-didehydro-somnifericin (**96**) [56], 17-*epi*-withanone (**41**) [57], pubesenolide (**105**) [58], 3-*O*-[β -D-glucopyranosyl (1 \rightarrow 6)- β -D-glucopyranosyl]-1 α ,3 β -dihydroxy-witha-5,24-dienolide (**110**) [43], withanoside X (**115**) [6], 6 α ,7 α -epoxy-1 α ,3 β ,5 α -trihydroxy-witha-24-enolide (**119**) [59], and withasomideone (**124**) [60], respectively (Table 1). Furthermore, by careful analysis of the published NMR data we were able to identify that the structures of ten withanolides (**58**, **59**, **83**, **85**, **86**, **87**, **93**, **101**, **103**, and **126**) (Figure 3) were inconclusive (Table 1).

In the 1960s, withanolide characterization was conducted through a combination of several methods including degradation chemistry, ^1H NMR, MS, IR, UV, and X-ray crystal diffraction as exemplified by the structural elucidation of withaferin A (**1**) [4, 22, 23].

In the 1970s, most withanolides reported were identified by MS, and comparison of their

^1H NMR values with those of published compounds. However, with the advent of ^{13}C NMR analysis in the 1970s, many withanolide structures were subsequently revised, as exemplified by the structure revisions of withanolides G-K, and U (**67-69**, **71**, **72**, and **80**) [32, 61, 62].

After the 1980s, additional withanolides were reported with the application of modern chromatographic separation tools and the advent of more powerful NMR techniques such as 2D-NMR.

The NMR spectroscopic data of the withanolides (**1-127**) were scattered all-over the vast phytochemical literature. Several recent reviews reported that structural elucidation of natural products is still error-prone, even though spectroscopic methods have become quite powerful in recent decades, due to the indirect nature of these techniques [63-66]. Our detailed investigation of the literature has shown that the reported structures of ten withanolides (**58**, **59**, **83**, **85**, **86**, **87**, **93**, **101**, **103**, and **126**) are inconsistent with their published NMR data. In addition, the structures of four withanolides (**58**, **59**, **93**, and **103**) should therefore be revised (Figure 6).

Withasomnilide (**58**) [67] was originally reported to have an unusual 6 β ,7 β -epoxy functionality and

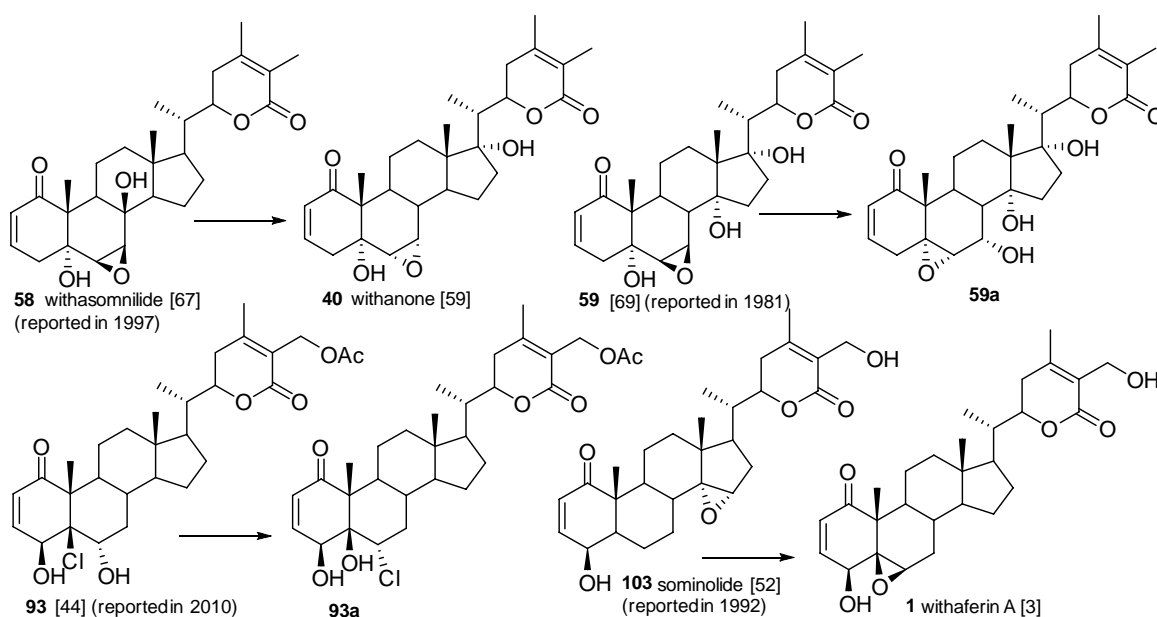


Figure 6. Inconsistent withanolide (**58**, **59**, **93** and **103**) structures and their respective revisions (**40**, **59a**, **93a**, and **1**).

an unusual hydroxyl group at C-8 (Figure 6). Since compound **58** and withanolide B (**38**) (Figure 3) share an identical ring D as well as the nine-carbon δ -lactone side chain, their ^{13}C NMR shifts for C-17 and C-20 to C-28 should exhibit similar values. However, upon examination of the reported ^{13}C NMR data for C₁₇, C₂₀, and C₂₁ revealed differences in excess of 2 ppm between **58** [C₁₇ 48.7, C₂₀ 36.8, and C₂₁ 15.6 ppm in CDCl₃] [67] and **38** [C₁₇ 51.5, C₂₀ 39.0, and C₂₁ 13.3 ppm in CDCl₃] [68]. These observed discrepancies questioned the validity of the published structure of **58**. Further comparison of the NMR data of **58** with those of other withanolides reported in the literature showed that the data of **58** are superimposable (supporting information Figure S1 and Table S1) with those of withanone (**40**) [62, 69], one of the main components in the same species. This analysis suggests that **58** is most likely to be **40** (Figure 6).

In the same publication, the assignment of **58** was utilized for the structural elucidation of three additional withanolides (withasomniferanolid **85**, somniferanolid **86**, somniferawithanolide **87**) (Figure 6). These compounds (**85-87**) were reported to also contain identical hydroxyl groups at C-8 [67]. However, the original assignment of

58 is incorrect; therefore the reported structures of **85-87** are also in need of revision (Figure 7).

Moreover withanolides **85-87** share an identical 1-oxo-2,5-diene moiety with those observed in withanolides F-I (**66-69**) (Figure 3). However, the ^{13}C NMR shifts (ppm) of C₁ to C₆, for **85-87** (C₁ 201.0, C₂ 126.3, C₃ 149.2, C₄ 33.6, C₅ 139.8, C₆ 128.7) [67] show a 2-5 ppm difference from those corresponding to withanolides **66-69** with a 1-oxo-2,5-dien moiety (C₁ 203.1, C₂ 127.0, C₃ 146.4, C₄ 32.9, C₅ 135.1, C₆ 125.1) [62, 70].

In the same publication [67] somniwithanolide (**101**) was reported to contain a 1-oxo-2,4-dien structural moiety. However, the ^{13}C NMR shift (ppm) of C₁ for **101** (C₁ 202.4) is more than 4 ppm different from those of other withanolides containing a 1-oxo-2,4-dien structural moiety, such as withametelins B (C₁ 206.8) [71]. Whereas the ^{13}C NMR shifts of C₂ to C₅ are similar (**101**: C₂ 119.6, C₃ 140.9, C₄ 128.4, and C₅ 160.1; withametelins B: C₂ 119.6, C₃ 141.5, C₄ 128.4, and C₅ 159.6). Based on the above information, the structure of **101** is inconsistent with its published NMR data (Figure 7).

Withanolide **59** was reported to have an unusual $6\beta,7\beta$ -epoxy functionality [69], having the following

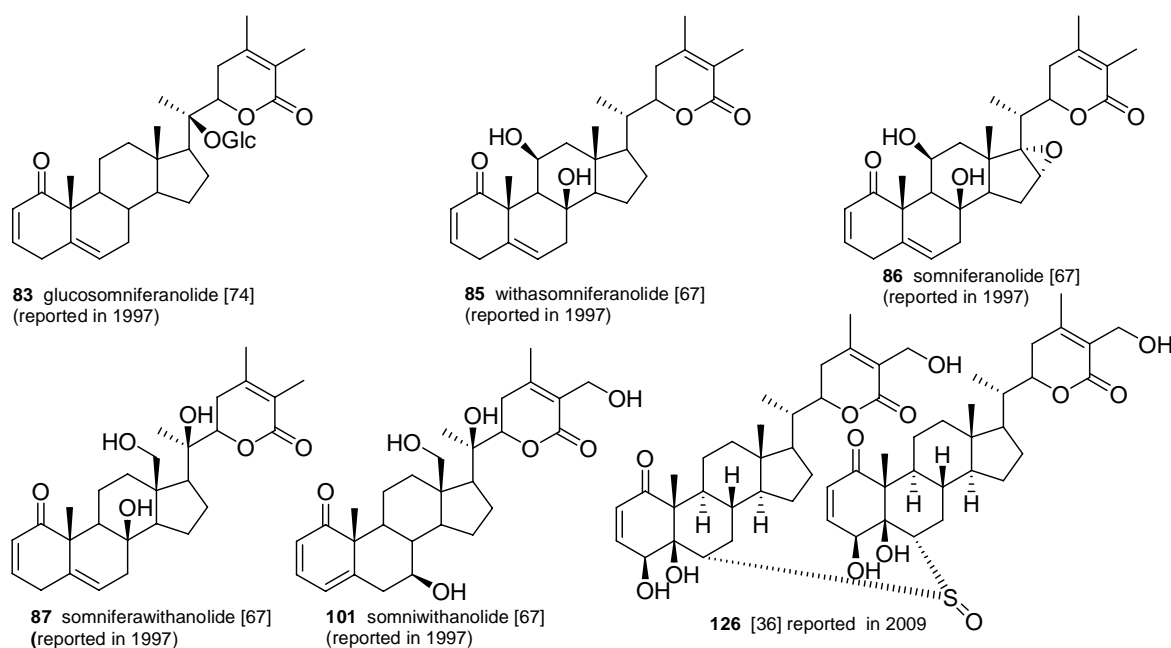


Figure 7. Additional inconsistent withanolide structures (**83**, **85**, **86**, **87**, **101**, and **126**).

^1H NMR data: (1) the low frequency chemical shifts of two mutual coupling protons at δ 3.72 (1H, d, $J = 4.0$ Hz) and δ 3.79 (1H, m); (2) the chemical shift of the C-19 methyl group at δ 1.32 (3H, s); and (3) the chemical shifts of H₂-4 at δ 3.19 (1H, d, $J = 19.5$ Hz) and 2.15 (1H, dd, $J = 19.0, 5.0$ Hz). The observed data were markedly different from those of withanone (**40**) [59], which contains a 5 α -hydroxy-6 $\alpha,7\alpha$ -epoxy moiety. This led to the original authors to propose the presence of a 6 $\beta,7\beta$ -epoxy moiety in withanolide **59** [69].

At first glance, the proton assignment of high frequency shift at δ 3.79 (1H, m) for H-7 in the 6 $\beta,7\beta$ -epoxy functionality initiated concern about the structure of **59**. Furthermore, these proton signal observations do not necessitate the presence of a 6 $\beta,7\beta$ -epoxy moiety. On the other hand, the ^1H NMR data for **59** were similar (supporting information Figure S2 and Table S2) to those of withanolide Y (**61**) - a withanolide containing a 5 $\alpha,6\alpha$ -epoxy-7 α -hydroxyl structural moiety confirmed by X-ray diffraction experiments [27]. The corresponding ^1H NMR data for **61** are: (1) the low frequency shifts of two mutual coupling protons at δ 3.36 (H-6, 1H, d, $J = 5.0$ Hz) and δ 3.91 (H-7, 1H, dd, $J = 11.0, 5.0$ Hz); (2) the chemical shift of the C-19 methyl group at δ 1.32 (3H, s); and (3) the chemical shifts of H₂-4 at δ 3.10 (1H, dt, $J = 20.0, 2.5$), 1.93 (1H, dd, $J = 20.0, 5.0$ Hz). Based on this information, the structure of **59** is more likely to be 20-deoxy-14 α -hydroxy-withanolide Y (5 $\alpha, 6\alpha$ -epoxy-7 $\alpha,14\alpha,17\alpha$ -trihydroxy-1-oxo-witha-2,24-dienolide) (**59a**) (Figure 6).

Withanolide **93** (27-acetoxy-5 β -chloro-4 $\beta,6\alpha$ -dihydroxy-1-oxo-witha-2,24-dienolide) was recently reported to bear a 5 β -chloro-4 $\beta,6\alpha$ -dihydroxy structural moiety [44]. This is vastly different to the commonly encountered 6 α -chloro-4 $\beta,5\beta$ -dihydroxy functionality as observed in withanolides **91, 92, 94** (Figure 3).

The chlorine at C₅ and the hydroxyl at C₆ in **93** were proposed by chemical shift arguments (C₅ 79.6 and C₆ 65.9) as well as by HMBC correlations in the literature [44]. Since C₅ and C₆ are a quaternary carbon, and a methine group, respectively, therefore, chemical shift arguments and HMBC correlations on their own supply insufficient information to propose the assignment of chlorine and hydroxyl groups in these positions. Furthermore, it has been reported that a

6 α -chloro-4 $\beta,5\beta$ -dihydroxy functionality (rather than the 5 β -chloro-4 $\beta,6\alpha$ -dihydroxy proposed in **93**) would be formed during the biogenic epoxy cleavage of 4 β -hydroxyl withanolides [72]. This initiated concern about the structure of **93**. In fact, the ^{13}C NMR data of rings A and B of **93** (C₁ 201.5, C₂ 126.5, C₃ 147.0, C₄ 64.8, C₅ 79.6, C₆ 65.9, C₇ 39.7, C₈ 35.3, C₉ 46.4, C₁₀ 58.1, C₁₉ 10.4 ppm in C₅D₅N) [44] are superimposable with those of a withanolide with a 6 α -chloro-4 $\beta,5\beta$ -dihydroxy functionality, namely anomolide D (C₁ 201.6, C₂ 126.1, C₃ 146.9, C₄ 64.6, C₅ 79.5, C₆ 65.8, C₇ 39.8, C₈ 35.0, C₉ 46.2, C₁₀ 58.1, C₁₉ 10.4 ppm in C₅D₅N) [73] (supporting information Figure S3 and Table S3). This suggested that withanolide **93** has a 6 α -chloro-4 $\beta,5\beta$ -dihydroxy rather than the reported 5 β -chloro-4 $\beta,6\alpha$ -dihydroxy functionality. Therefore, based on our analysis of the data, the structure of **93** was most likely to be 27-acetoxy-6 α -chloro-4 $\beta,5\beta$ -dihydroxy-1-oxo-witha-2,24-dienolide (**93a**) (Figure 6).

Sominolide (**103**) [52] was reported to have a 14 $\alpha,15\alpha$ -epoxy group but lacking any functionality at C₅ or C₆ (i.e., 5-ene, 5,6-epoxy, or 5,6-dihydroxy, or 5-hydroxy-6,7-epoxy). This information initiated concern about the correctness of the structure assignment of **103**. Literature investigation showed that the ^1H NMR data of **103** and withaferin A (**1**) are superimposable [4] (supporting information Figure S4 and Table S4). This suggests that **103** is more likely to be **1** (Figure 6).

The saponin, glucosomniferanolide **83** (20-*O*- β -D-glucopyranosyl-1-oxo-witha-2,5,24-trienolide) [74] (Figure 7), was reported to contain a sugar unusually attached to a highly sterically hindered carbon, specifically at C₂₀ in the side chain. This initiated concern about the correctness of the structure assignment of **83**. The reported ^{13}C NMR data of **83** (C₁ 202.8, C₂ 142.3, C₃ 127.1, C₄ 33.8, C₅ 127.1, C₆ 120.0, C₁₉ 14.2 ppm in CDCl₃) [74] is different from its aglycone, 20-hydroxy-1-oxo-witha-2,5,24-trienolide (C₁ 203.6, C₂ 127.9, C₃ 145.2, C₄ 33.4, C₅ 135.9, C₆ 124.7, C₁₉ 18.9 ppm in CDCl₃) [75]. The observed 5 ppm differences at C₃, C₅, C₆, and C₁₉ suggest that the reported structure of **83** [74] is also in need of revision (Figure 7).

The recently reported structure of a withanolide dimer (**126**) [36] (Figure 7), is evidently inconclusive

as it is inconsistent with its ^{13}C NMR data. As proposed in the literature, **126** is a symmetric withanolide, which is almost identical to another symmetric withanolide dimer, **125** [35] (Figure 3). Theoretically, 28 carbons should be observed in both **125** and **126**. However, 28 and 56 carbon signals were reported to be observed in **125** and **126**, respectively. It was concluded that the structure of withanolide **126** is also in need of structural revision.

Compound names, isolation sources, available ^1H , ^{13}C NMR spectroscopic and X-ray crystallography data, for the 127 withanolides are summarized in conjunction with corresponding literature references (Table 1) [76-124].

CONCLUSIONS

Ashwagandha is one of the most important medicinal herbs used in the Hindu traditional Ayurvedic system of medicine. Over the course of the past 50 years the phytochemical profile of this medicinal plant has been extensively investigated, however this information is scattered throughout a vast body of literature. Such exhaustive research has resulted in the isolation of 167 natural products (withanolides, alkaloids, phenolics), which led to the discovery that unmodified withanolides are the main active ingredients of the species. This article compiles

this research, and represents the first complete phytochemical compendium of the species.

Among the reported 127 withanolides, we observed that the published NMR values revealed inconsistent data related to ten withanolide structures (**58**, **59**, **83**, **85**, **86**, **87**, **93**, **101**, **103** and **126**). Four withanolides [withasomnilide (**58**), $6\beta,7\beta$ -epoxy- $5\alpha,14\alpha,17\alpha$ -trihydroxy-1-oxo-witha-2,24-dienolide (**59**), 27-acetoxy- 5β -chloro- $4\beta,6\alpha$ -dihydroxy-1-oxo-witha-2,24-dienolide (**93**), and sominolide (**103**)] were found to possess identical NMR data assigned to those of other withanolides [withanone (**40**), 20-deoxy- 14α -hydroxy-withanolide Y (**59a**), 27-acetoxy- 6α -chloro- $4\beta,5\beta$ -dihydroxy-1-oxo-witha-2,24-dienolide (**93a**), and withaferin A (**1**), respectively]. It is our belief that the information presented here will be indispensable in the continuing exploration of this traditional botanical remedy.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. Cong-Mei Cao and Mr. Robert J. Gallagher for their assistance in the preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

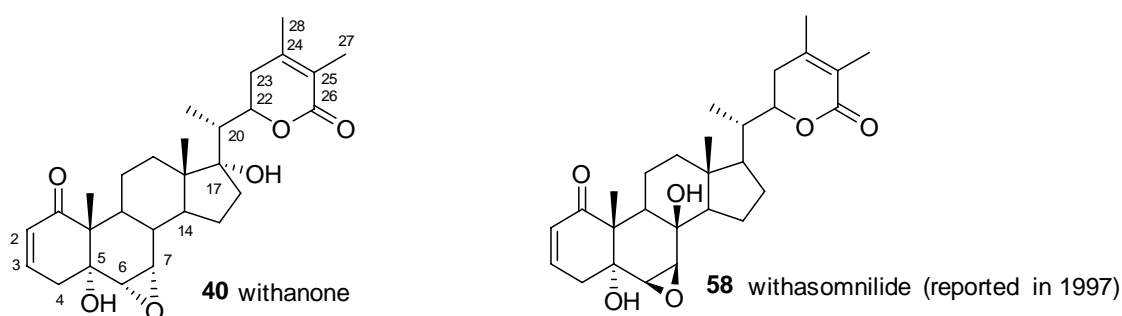


Figure S1. Withanolides compared using ^1H and ^{13}C NMR data in Table S1.

Table S1. Comparison of ^1H and ^{13}C NMR data (ppm, in CDCl_3) of withanone (**40**) and withasomnilide (**58**).

Num.	40 withanone		58 withasomnilide ^a	
	^{13}C [62, 69]	^1H [59]	^{13}C [67]	^1H [67]
1	202.7		203.0	
2	129.0	5.81 (1H, dq, $J = 10.0, 3.0, 1.0$ Hz)	129.0	5.73 (1H, d, $J = 10.0$ Hz)

Table S1 continued..

3	140.7	6.60 (1H, dq, $J = 10.0, 4.5, 3$ Hz)	139.6	6.60 (1H, m)
4	37.1		<u>36.7</u>	
5	73.7		73.2	
6	56.4	3.06 (1H, d, $J = 4.0$ Hz)	56.3	3.00 (1H, d, $J = 10.0$ Hz)
7	57.1	3.34 (1H, dd, $J = 4.0, 1.0$ Hz)	57.1	3.10 (1H, d, $J = 10.0$ Hz)
8	36.3		<u>36.1</u>	
9	35.4		<u>35.3</u>	
10	51.4		51.0	
11	22.0		21.7	
12	37.1		36.8	
13	49.0		<u>48.7</u>	
14	46.0		45.9	
15	23.1		22.9	
16	33.0		32.8	
17	84.6		<u>84.6</u>	
18	15.2	0.85 (3H, s)	<u>15.6</u>	0.83 (3H, s)
19	14.9	1.18 (3H, s)	14.7	1.16 (3H, s)
20	43.5		<u>43.0</u>	1.55 (1H, br s)
21	9.6	1.04 (1H, d, $J = 7.0$ Hz)	<u>9.5</u>	1.00 (3H, d, $J = 7.0$ Hz)
22	79.6	4.63 (1H, dt, $J = 8.0, 5.0, 3.0$ Hz)	78.8	4.46 (1H, m)
23	32.6		32.5	
24	152.0		150.3	
25	121.4		121.4	
26	168.4		167.3	
27	12.3	1.90 (3H, s)	12.3	1.86 (3H, s)
28	20.6	1.90 (3H, s)	20.4	1.86 (3H, s)

^aNote: The numbers with an underline mean that the assignments reported [67] were switched.

Conclusion: The superimposable NMR data of these two withanolides showed that the structure of **58** ($6\beta,7\beta$ -epoxy- $5\alpha,8\beta$ -dihydroxy-1-oxo-witha-2,24-dienolide) is most likely **40** ($6\alpha,7\alpha$ -epoxy- $5\alpha,17\alpha$ -dihydroxy-1-oxo-witha-2,24-dienolide).

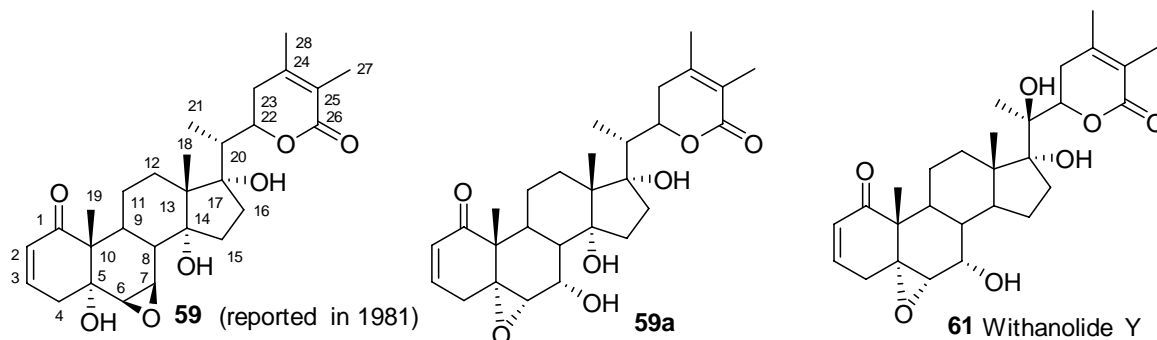


Figure S2. Withanolides compared using ¹H NMR data in Table S2.

Table S2. Comparison of ^1H NMR data (ppm in CDCl_3) of **59** and withanolide Y (**61**).

Number of ^1H position	59	61
	^1H [69]	^1H [27]
2	5.83 (1H, d, $J = 9.4$ Hz)	5.98 (1H, dd, $J = 10.0, 3.0$ Hz)
3	6.61 (1H, m)	6.72 (1H, ddd, $J = 10.0, 5.0, 2.5$ Hz)
4	3.19 (1H, d, $J = 19.5$ Hz), 2.15 (1H, dd, $J = 19.0, 5.0$)	3.10 (1H, dt, $J = 20.0, 2.5$), 1.93 (1H, dd, $J = 20.0, 5.0$ Hz)
6	3.72 (1H, d, $J = 4.0$ Hz)	3.36 (1H, d, $J = 5.0$ Hz)
7	3.79 (1H, m)	3.91 (1H, dt, $J = 11.0, 5.0$ Hz)
18	0.86 (3H, s)	0.83 (3H, s)
19	1.32 (3H, s)	1.33 (3H, s)
20		1.55 (1H, br s)
21	1.07 (1H, d, $J = 6.3$ Hz)	1.27 (3H, s)
22	4.64 (1H, m)	4.51 (1H, dd, $J = 13.5, 3.5$ Hz)
27	1.86 (3H, s)	1.87 (3H, s)
28	1.96 (3H, s)	1.94 (3H, s)

Note: The structure of withanolide Y (**61**) was confirmed by X-ray diffraction crystallography [27].

Conclusion: The ^1H NMR data of rings A and B of **59** ($6\beta,7\beta$ -epoxy- $5\alpha,14\alpha,17\alpha$ -trihydroxy-1-oxo-witha-2,24-dienolide) are in good agreement with those of **61** ($5\alpha,6\alpha$ -epoxy- $7\alpha,20$ -dihydroxy-1-oxo-witha-2,24-dienolide). This suggested that **59** and **61** share identical rings A and B structural moieties. The structure of **59** reported in the literature is more likely 20-deoxy- 14α -hydroxy-withanolide Y ($5\alpha,6\alpha$ -epoxy- $7\alpha,14\alpha,17\alpha$ -trihydroxy-1-oxo-witha-2,24-dienolide) (**59a**).

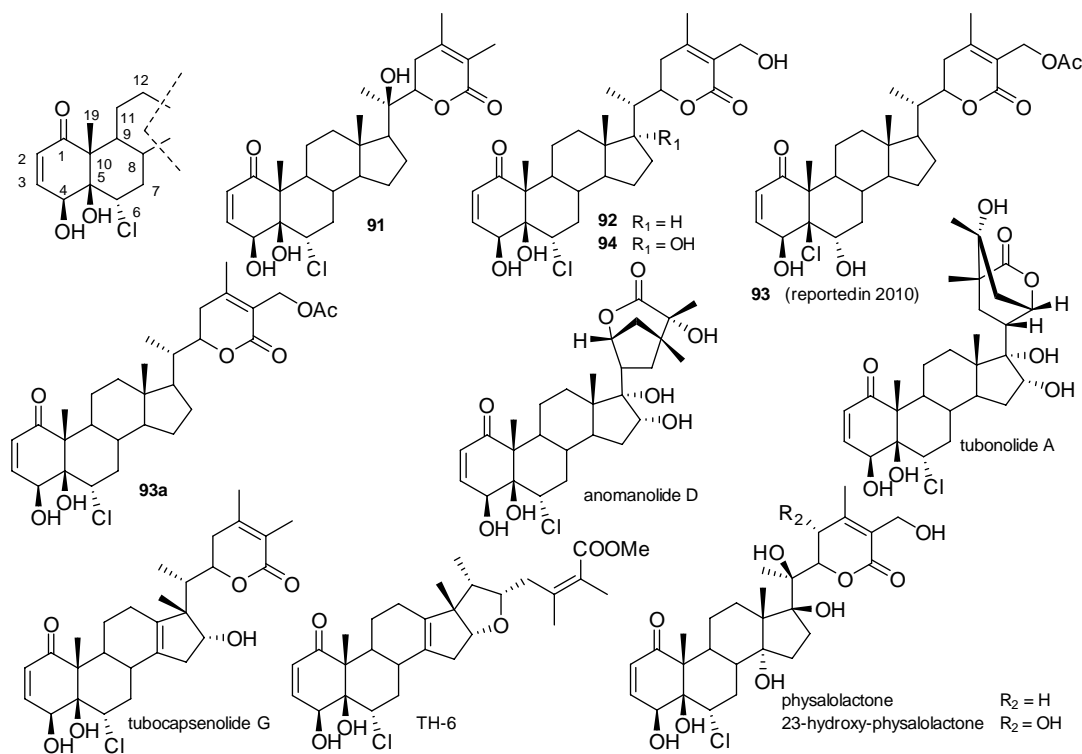
**Figure S3.** Withanolides compared using ^{13}C NMR data in Table S3.

Table S3. Comparison of ^{13}C NMR data (ppm) of the rings A and B of **91-94**, anomanolid D, tubocapsenolid A, tubocapsenolid G, TH-6, physalolactone, and 23-hydroxy-physalolactone[#].

Number of carbon position	91^a [42]	92^a [25, 42]	93^b [44]	anomanolide D^b [73]	tubonolide A^b [73]	TH-6 ^c [125]	tubocapsenolid e^c [73]	94^a [25]	Physalolactone ^c [126]	23-hydroxy-physalolactone ^c [126]
1	201.1	200.1	201.5	201.6	202.0	200.2	200.0	200.2	203.8	203.6
2	127.7	127.8	126.5	126.1	126.7	127.6	127.7	127.8	126.9	126.8
3	143.1	142.8	147.0	146.9	147.4	143.2	143.2	142.8	147.6	147.5
4	66.0	66.2	64.8	64.6	65.2	66.5	66.1	66.1	66.0	65.8
5	78.3	78.1	79.6	79.5	80.0	78.2	78.2	78.1	80.0	80.0
6	66.2	66.7	65.9	65.8	66.3	66.9	66.8	66.5	66.0	66.0
7	39.1	39.4	39.7	39.8	40.3	38.5	38.1	39.3	35.7	35.8
8	34.5	35.1	35.3	35.0	35.7	36.1	36.0	35.2	40.1	40.0
9	45.7	45.8	46.4	46.2	46.7	46.1	43.3	45.3	39.9	39.9
10	57.2	57.2	58.1	58.1	58.6	57.1	57.1	57.1	58.3	58.3
11	22.5	22.7	23.9	22.6	23.1	24.1	24.0	22.4	23.8	23.7
19	9.9	9.9	10.4	10.4	10.9	10.0	10.4	9.9	9.7	9.8

[#]The structures of **94** [25], TH-6 [125] and tubocapsenolid G [73] were confirmed by X-ray crystallography.

^aMeasured in CDCl_3 , ^bmeasured in $\text{C}_5\text{D}_5\text{N}$, ^cmeasured in CD_3OD .

Conclusion: The similar ^{13}C NMR data of the carbons (C_1 - C_{11} , C_{19}) on rings A and B of the withanolides (**91-94**, anomanolid D, tubonolide A, tubocapsenolid G, TH-6, physalolactone, and 23-hydroxy-physalolactone) with a 6 α -chloro-4 β ,5 β -dihydroxy functionality, especially the superimposable data of **93** (27-acetoxy-5 β -chloro-4 β ,6 α -dihydroxy-1-oxo-witha-2,24-dienolide) and anomanolid D (both measured in $\text{C}_5\text{D}_5\text{N}$, and the shifts discrepancy of C-1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 19 is less than 0.5 ppm), showed that **93** has a 6 α -chloro-4 β ,5 β -dihydroxy functionality instead of the reported 5 β -chloro-4 β ,6 α -dihydroxy moiety. The structure of **93** is most likely to be 27-acetoxy-6 α -chloro-4 β ,5 β -dihydroxy-1-oxo-witha-2,24-dienolide (**93a**).

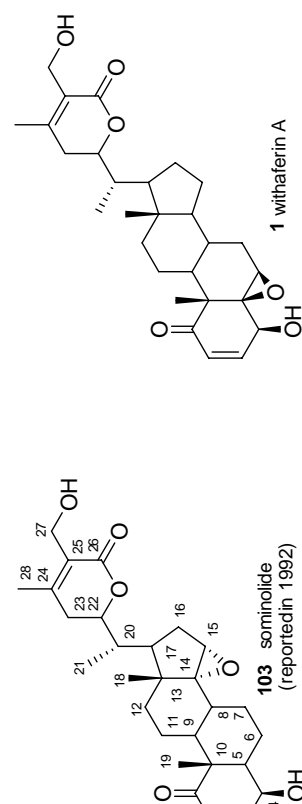
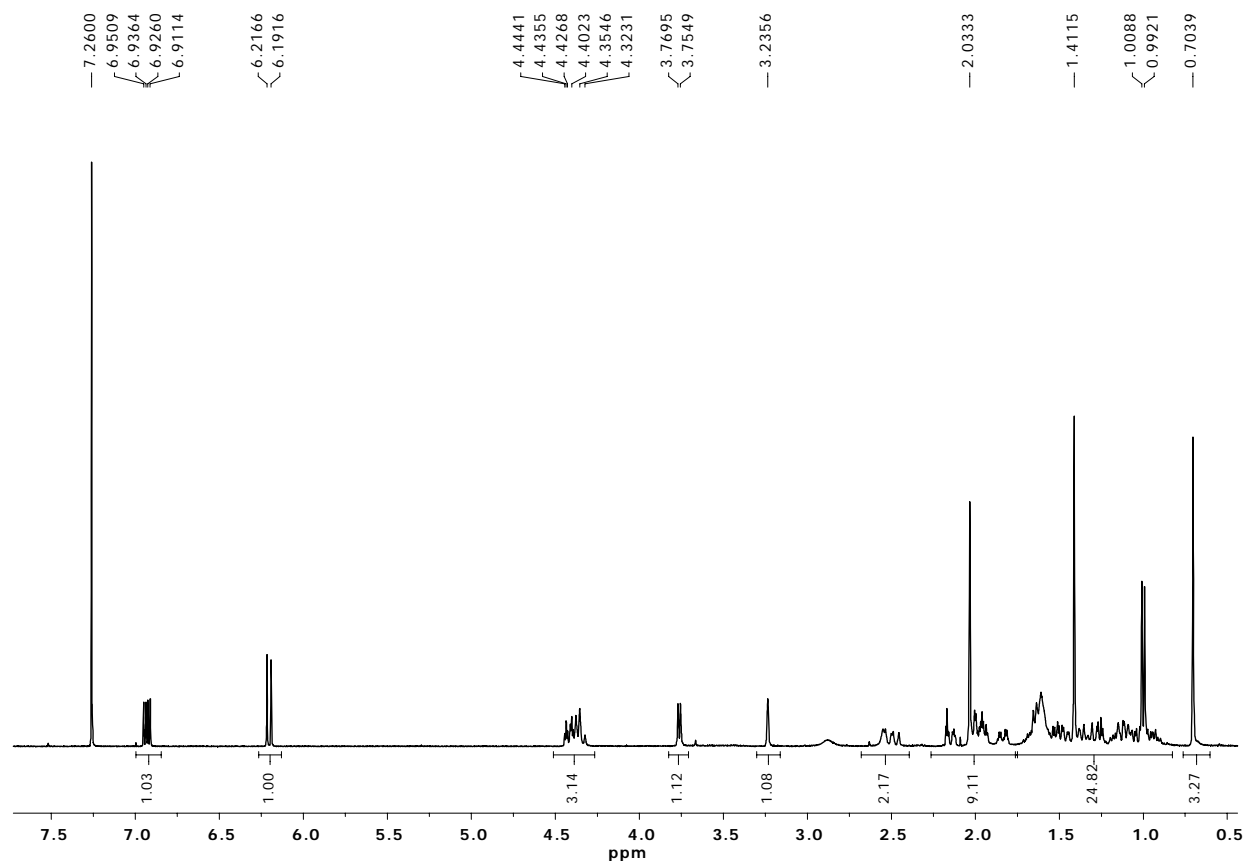
**Figure S4.** Withanolides compared using ^1H NMR data in Table S4.

Table S4. Comparison of ^1H NMR data (ppm in CDCl_3) of sominolide (**103**) and withaferin A (**1**).

Number of ^1H position	103 sominolide [#] [52]	1 withaferin A [4]	
		Data from reference [13]	Data from our experiment (Figure S5)
2	6.19 (1H, d, $J = 9.9$ Hz)	6.18 (1H, d, $J = 10$ Hz)	6.20 (1H, d, $J = 10$ Hz)
3	6.92 (1H, dd, $J = 9.9, 5.8$ Hz)	6.97 (1H, dd, $J = 10.0, 6.0$ Hz)	6.93 (1H, dd, $J = 10.0, 5.8$ Hz)
4	3.76 (1H, dd, $J = 5.8, 2.5$ Hz)	3.75 (1H, dd, $J = 6.0$ Hz)	3.76 (1H, d, $J = 6.6$ Hz)
6	3.22 (1H, brs)	3.20 (1H, brs)	3.24 (1H, brs)
18	0.71 (3H, s)	0.71 (3H, s)	0.70 (3H, s)
19	1.41 (3H, s)	1.38 (3H, s)	1.41 (3H, s)
21	1.00 (1H, d, $J = 6.7$ Hz)	0.97 (1H, d, $J = 6.5$ Hz)	1.00 (1H, d, $J = 6.5$ Hz)
22	4.44 (1H, ddd, $J = 13.2, 5.1, 3.5$ Hz)	4.40 (1H, dt, $J = 13.5, 4.0$ Hz)	4.43 (1H, dt, $J = 13.5, 3.5$ Hz)
27	4.36 (2H, d, $J = 12.7$ Hz)	4.35 (2H, d, $J = 12.7$ Hz)	4.36 (2H, d, $J = 12.6$ Hz)
28	2.03 (3H, s)	2.03 (3H, s)	2.03 (3H, s)

[#]The NMR signal of H-4 in the literature [52] was typed incorrectly as 3.95 ppm because the ^1H NMR spectrum in the same paper [52] showed that the chemical shift of H-4 was 3.75 ppm.

**Figure S5.** ^1H NMR spectrum of withaferin A (**1**) in CDCl_3 (400 MHz).

Conclusion: The superimposable ^1H NMR data of sominolide (14 α ,15 α -epoxy-4 β ,27-dihydroxy-1-oxo-witha-2,24-dienolide) (**103**) and withaferin A (**1**) showed that the structure of **103** is more likely **1**.

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