Herbal Drugs as Therapeutic Agents

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Preface

The chief aim of writing a book titled *Herbal Drugs as Therapeutic Agents* is to highlight the contribution of herbal drugs to pharmacology and in drug discovery. My previous book on *Herbalism, Phytochemistry and Ethnopharmacology* was well received and this motivated me to write a book on therapeutic scope of herbal drugs. Several herbal drugs and isolated constituents have entered clinical trials in recent times and positive outcomes have been reported.

Herbal medicine is going to play a significant role in future healthcare industry. In the past, medicinal plants have provided us with life-saving drugs, particularly in oncology. To name a few—atropine, digoxin, morphine, paclitaxel, pilocarpine, reserpine, scopolamine, topotecan and vincristine. However, several of these compounds have outlived their usefulness in light of better alternatives.

Herbal medicine is interdisciplinary subject and the expert herbal scientist blends traditional herbal medicine with botany, ethnobotany, phytochemistry, pharmacognosy, pharmacology and allopathic medicine. A large part of the world's population depends upon traditional herbal medicine for their daily health requirements, especially in developing countries. Even in industrialized countries the use of plant-based remedies is widespread and numerous pharmaceuticals are based on or derived from plant compounds.

The book starts with a chapter on reported pharmacological activities of withanolides, followed by a chapter targeting anticancer role of withaferin A. The chapter on CAM studies some common anticancer therapies. Succeeding chapters throw light on pharmacological investigations on berberine, protopine, piperine, liriodenine, andrographolide, hypericin, hyperforin and above all, anthrquinones. A chapter has been dedicated to alkaloids from Indian medicinal plants and data on pharmacological investigations.

The chapter on anti-arthritic and anti-acne drugs reviews drugs that are beneficial for treatment of arthritis and acne vulgaris. Pharmacological

investigations on Indian nootropic, *Convolvulus plauricaulis* Linn. and anticancer plant,*Viscum album* Linn.- have also been covered.

The author trusts that the present book will meet the long-felt need for a standard book on herbal therapeutics. The author shall be grateful to readers for pointing out any errors that may be there.

Amritpal Singh

List of the Abbreviations

µg	:	a microgram
µM	:	The micrometre
EC50	:	half maximal effective concentration
ED50	:	*In vitro* or *in vivo* dose of drug that produces 50% of its maximum response or effect
Ex vivo	:	Taking place outside a living organism
G2-M	:	cell cycle phase
i.d.	:	Intradermal route of drug administration
i.g.	:	Intragastric route of drug administration
i.l.	:	Intralesional injection
i.m.	:	Intramascular route of drug administration
i.v.	:	Intravenous
IC50	:	The half maximal inhibitory concentration
In vitro	:	Taking place in a test-tube, culture dish or elsewhere outside a living organism
In vivo	:	Taking place in a living organism
IP	:	Intraperitoneal injection
PO	:	Oral (by mouth) route of drug administration
SC	:	Subcutaneous route of drug administration

Contents

Chapter 1

Withanolides—Phytoconstituents with Significant Pharmacological Activities

1.1 INTRODUCTION

About 50 new withanolides have been found in plants, mainly in the roots and leaves, during the year (Table 1.1). Lavie et al., in 1965 studied the basic structure of withanolides. Chemically, they are a group of naturally occurring oxygenated ergostane type steroids (Fig. 1.1), consisting of lactone in the side chain and 2-en-1-one system in ring A.[1]

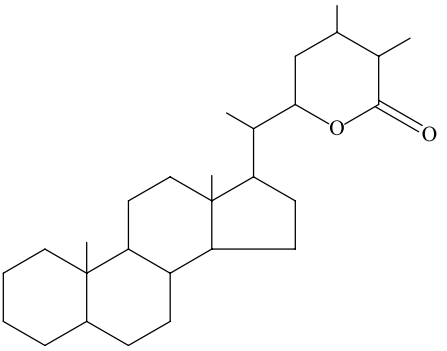

Figure 1.1 Basic withanolide skeleton.

Many are saponins containing an additional acyl group; the rest have glucose at carbon 27.[1] This class of steroid derivative is largely restricted in distribution to the genera *Acnistus*, *Datura*, *Discopodium*, *Dunalia*, *Jaborosa*, *Lycium*, *Nicandra*, *Physalis*, *Solanum*, and *Withania*, all belonging to the plant family Solanaceae.[2]

1.2 PREVIOUS REPORTED WORK

Earlier 1α, 3β, 20-trihydroxy witha-5, 24-dienolide and 7α, 27-hydroxy-1-oxo-witha-2, 5-24-trienolide and 7α, 27-dihydroxy-1-oxo- witha-2, 5-24-trienolide were reported from *W. somnifera* chemotype 3.[3] Two minor constituents, 7α, 27-hydroxy-1-oxo-witha-2,5,24-trienolide and 7α, 27-dihydroxy-1-oxo-witha-2,5,24-trienolide have been found in the Indian chemotype of *W. somnifera*.[4] Three withanolides G (Fig. 1.2), H and J, along with 20-hydroxy-1-oxo-witha-2,5,16,24-trienolide have been reported from *W. somnifera* chemotype III.[5-7] Three withanolides I, J and K have been isolated from *W. somnifera* chemotype III.[5] Withanolide U was reported from *W. somnifera* chemotype III.[8]

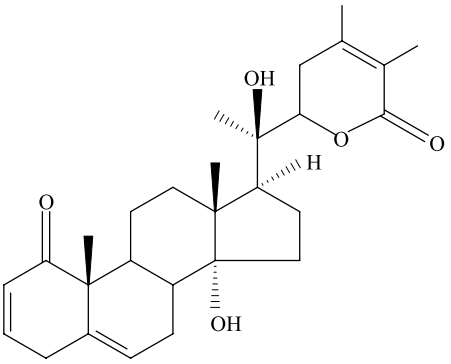

Figure 1.2 Structure of withanolide G.

Withaferin A (Fig. 1.3) was the first compound isolated as a major compound in *W. somnifera* chemotype I.[1] 27-deoxy-withaferin (Fig. 1.4) was also reported to contain withaferin A.[9] Withaferin A is thought to be the primary pharmacological agent present in the roots and leaves of *W. somnifera*.[10,11]

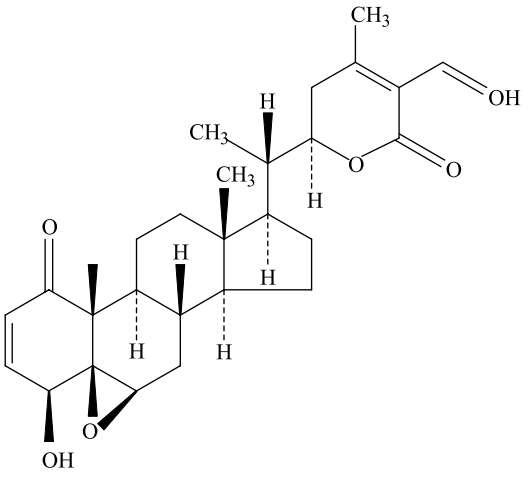

Figure 1.3 Structure of withaferin A.

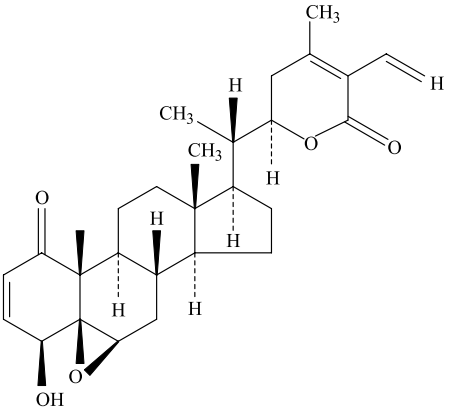

Figure 1.4 Structure of 27-deoxywithaferin A.

Withanolide D (Fig. 1.5) has been reported from *W. somnifera* chemotype II.[12] Several withanolides such as chlorohyrdin II, 27-O-glucosides (sitoinoside IX and X), and withasomidienone (Fig. 1.6) have been characterized from the roots of *W. somnifera*.[13,14] In the Indian chemotype of *W. somnifera*, jaborosalactone A (Fig. 1.7) and withanolide Y have been isolated.[3,15] Two withanolides, Q and R have been reported from the offspring of Indian chemotype 1 and 3 of *W. somnifera*.[16]

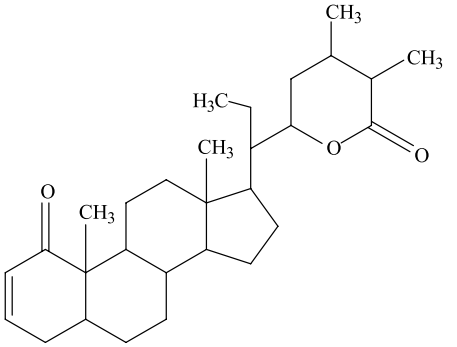

Figure 1.5 Structure of withanolide D.

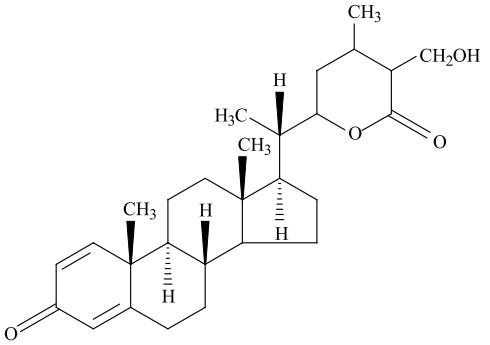

Figure 1.6 Structure of withasomidienone.

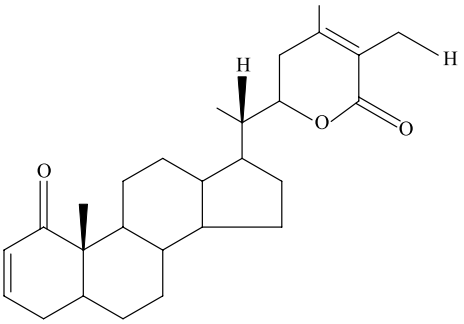

Figure 1.7 Structure of jaborosalactone A.

Withanolide F, E and 4β-hydroxy-withanolide E were isolated from *W. somnifera* chemotype III.[17,18] Furthermore, withanolide S and T have been reported from *W. somnifera* chemotype III.[19] A variety of withanolides including sominolide, soinone, withasomnilide, withasomniferabolide, somniferanolide and somnwithanolide have been reported in the stem bark of *W. somnifera.*[20-24]

1.3 RECENT ADVANCES IN PHARMACOLOGICAL ACTIVITIES

Previous studies reported anti-inflammatory, anti-arthritic, antibiotic, antitumor, immunomodulator and central nervous system effects of withanolides (Table 1.1).[25-37]

Table 1.1 Pre-clinical pharmacological activities of withanolides

Withanolide	*Biological Activity*	*Reference*
Withaferinil	Antitumor	Palyi et al., 1969
Withaferin A	Antitumor	Palyi et al., 1969; Chakrabotri et al., 1974; Ascher et al., 1981; Budhiraja et al., 1987
4β,20-dihydroxy-i-oxo-5β,6β,-epoxy-witha-2, 24-dienolide	Antitumor	Chakrabotri et al., 1974;
Compound WS-1	Hypno-sedative	Kundu et al., 1976
Withanolide -E	Antifeedent	Ascher et al., 1981
Withanolide-5,20α,(*R*) -dihydroxy-6α,7α-epoxy-1-oxo-5α -witha-2, 24-dienolide	Immunomodulator	Bahr et al., 1982
Withanolide-D	Antitumor	Das et al., 1985
3-β-hydroxy-2, 3-dihydro-withanolide	Antibacterial, antitumor, immunomodulator and anti-inflammatory	Budhiraja et al., 1987