Chapter 5
Guggulsterone: a Potent Natural Hypolipidemic Agent from Commiphora wightii – Problems, Perseverance, and Prospects

K.G. Ramawat (✉), M. Mathur, S. Dass and S. Suthar

Laboratory of Bio-Molecular Technology, Department of Botany, M. L. Sukhadia University, Udaipur-313001, India, e-mail: kg_ramawat@yahoo.com

Abstract  Two isomers of guggulsterone, -E and -Z, have been established as bioactive molecules responsible for the lipid- and cholesterol-lowering activities of oleogum-resin of Commiphora wightii (Arnott.) Bhandari (syn. C. mukul). Guggulsterone is a safe and effective natural product for hypercholesterolemia that has been used as such for the past 3000 years in Ayurveda. It is obtained from a very slow growing desert tree endemic to the Thar Desert and has become endangered due to its over exploitation. Oleogum-resin is a complex mixture of several classes of compounds including gum, minerals, essential oils, sterols, flavanones, and sterones. Early chemical and pharmacological work was carried out in India, but after approval by the United States Food and Drug Administration as a food supplement, several reports describe a role for guggulsterone in the excretion of cholesterol, involving the farnesoid X receptor, pregnane X receptor, Cyp-7A1 gene, and the bile salt export pump. Biotechnological approaches have been made to develop micropropagation methods through axillary bud break and somatic embryogenesis, as well as guggulsterone production through cell cultures grown in shake flasks and bioreactors. Field-grown plants show genetic variations, as evident by randomly amplified polymorphic DNA fingerprinting. This review summarizes the research already carried out and that needs to be done to elucidate the biosynthetic pathway, mechanism of action, and biotechnological production of guggulsterone through cell cultures before commercialization of the molecule as a drug.

Keywords  Commiphora wightii, C. mukul, Guggulsterone, Farnesoid X receptor, Micropropagation, Somatic embryogenesis, Production of secondary metabolite
Abbreviations

2iP  2-Isopentenyl adenine
CAR  Constitutive androgen receptor
FXR  Farnesoid X receptor
HPLC High performance liquid chromatography
LDL  Low-density lipoproteins
LPO  Lipid peroxidation
MS   Murashige and Skoog’s
PXR-Ko  Pregnane X receptor
T3   Tri-iodothyronine

5.1 Introduction

The two closely related steroidal ketones, guggulsterone-E (pregna-4,17-diene-3,16-dione) and guggulsterone-Z, are the potent hypolipidemic and hypocholesterolemic bioactive molecules present in the gum resin of *Commiphora wightii* (Arnott.) Bhandari (Syn. *C. mukul*, *Balsamadendron mukul*). *C. wightii* is a slow-growing, woody, endangered medicinal tree, indigenous to Indian subcontinent, belonging to the family Burseraceae and having the chromosome number 2n=26 [1]. Since it is a very slow growing plant, the returns from the plant are only after several years and thus, not preferred for social forestry. Besides gum-resin, nothing is obtained as forest produce from this plant.

5.2 Distribution

*Commiphora* species are widely distributed in tropical regions of Africa, Madagascar, and Asia. It is generally distributed in arid regions of Africa and the Indian side of Thar Desert. In the Indian subcontinent, *Commiphora* species occur in Pakistan, Baluchistan, and India. Of the total 185 species, only 3 (*C. wightii*, *C. stocksii*, and *C. berryi*) have been found in India. *C. wightii* occurs in Rajasthan, Gujrat, and Maharashtra [1].

5.3 Biology

A characteristic feature of the family is the presence of resin ducts in the parenchymatous bark. The plant is a shrub that reaches 3m in height and has crooked, knotty branches ending in sharp spines. The papery bark peels in flakes from the older parts of the stem, whereas younger parts are pubescent and glandular leaves are trifoliate. Gupta et al. [2, 3] reported apomictic seed