Guggulsterone and Its Role in Chronic Diseases

Takanori Yamada and Ken Sugimoto

Abstract Guggulsterone is a plant sterol derived from gum resin of *Commiphora wightii*. The gum resin from guggul plants has been used for thousand years in Ayurveda to treat various disorders, including internal tumors, obesity, liver disorders, malignant sores and ulcers, urinary complaints, intestinal worms, leucoderma, sinuses, edema, and sudden paralytic seizures. Guggulsterone has been identified a bioactive components of this gum resin. This plant steroid has been reported to work as an antagonist of certain nuclear receptors, especially farnesoid X receptor, which regulates bile acids and cholesterol metabolism. Guggulsterone also mediates gene expression through the regulation of transcription factors, including nuclear factor-kappa B and signal transducer and activator of transcription 3, which plays important roles in the development of inflammation and tumorigenesis. Guggulsterone has been shown to downregulate the expression of proteins involved in anti-apoptotic, cell survival, cell proliferation, angiogenic, metastatic, and chemoresistant activities in tumor cells. This review aimed to clarify the cell signal pathways targeted by guggulsterone and the bioactivities of guggulsterone in animal models and humans.

Keywords Guggul · Guggulsterone · Cancer · Inflammation · Hyperlipidemia · Chemoprevention

T. Yamada (✉)
Department of Gastroenterology, Iwata City Hospital, 512-3, Okubo, Iwata 438-8550, Japan
e-mail: tky@hospital.iwata.shizuoka.jp

K. Sugimoto
First Department of Medicine, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan

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1 Introduction

Cancers or vascular events are major causes of death all over the world. Both of these critical conditions are considered to be associated with chronic inflammation and obesity. In spite of huge efforts to control them, these disorders are still highly prevalent. Generally, modern medicines tend to be mono-targeted, focusing on a single gene product or pathway. However, most chronic diseases develop and progress in a multistep process. The discrepancy between the design concept of modern medicine and disease progression processes may be one of the reasons why modern medicine has not yet overcome these disorders.

Guggul is one of the very ancient Ayurvedic drugs and has been used for several thousand years. Guggulsterone is the major bioactive compound of guggul. According to the Sushruta Samhita, a well-known Ayurvedic medical text, guggul when taken orally, is a curative for obesity, liver disorder, internal tumors, malignant sores and ulcers, urinary complaints, fistula-in-ano, intestinal worms, leucoderma, sinus, edema, and sudden paralytic seizures [77, 84]. It has been revealed that guggulsterone acts as an antagonist of the farnesoid X receptor (FXR) and has hypolipidemic effects [97]. Guggulsterone has also been reported to inhibit pro-inflammatory signals, including transcription factor nuclear factor-kappa B (NF-κB) [82]. Furthermore, guggulsterone suppressed tumor progression in multistep cell growth, proliferation, invasion, metastasis, and angiogenesis. This review describes the cell signaling pathways targeted by guggulsterone and its bioactivities in animal models and humans [85].

2 Physicochemical Properties of Guggulsterone

The guggul tree (*Commiphora mukul*) is native to India and its neighboring countries. The oleogum resin of this species is a yellowish substance that is tapped during winter, and each tree yields about 700–900 g of resin [76]. Guggul is a complex mixture of gum, minerals, essential oils, terpenes, sterols, ferrulates, flavanones, and sterones. When extracted with ethyl acetate, the extraction yields two fractions: 45 % soluble and 55 % insoluble fractions. The bioactive components found in the ethyl acetate soluble fraction, known as gugulipid, consist of diterpenoids, triterpenoids, steroids, lignans, and fatty tetrol esters. Further fractionation of the soluble fraction with pH gradients yielded a 4 % acidic fraction, 1 % basic fraction, and 95 % neutral fraction. Additional fractionation of the neutral fraction led to the isolation of a major nonketonic (88 %) and a small ketonic fraction (12 %). The ketonic fraction contained a number of steroids including the two isomers E-(*cis*-) and Z-(*trans*-)guggulsterone (4, 17(20)-pregnadiene-3, 16-dione)

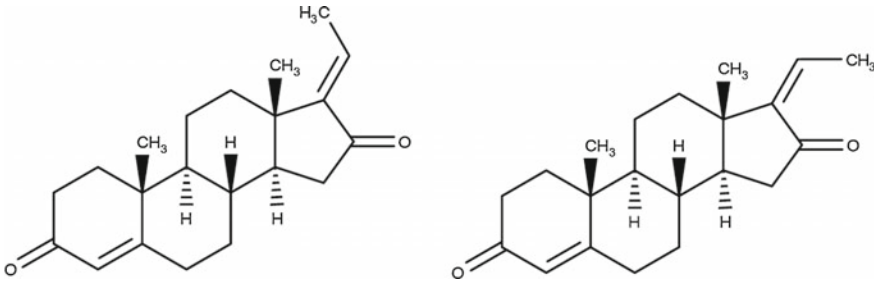

Fig. 1 Chemical structure of guggulsterone isomers. **a** [4,17[20]-(*cis*)-pregnadiene-3,16-dione] is E-guggulsterone. **b** [4,17[20]-(*trans*)-pregnadiene-3,16-dione] is Z-guggulsterone

(Fig. 1). The guggulsterones constitute approximately 2 % of gum guggul and 5 % of gugulipid by weight [19, 83].

Molecular docking simulation studies reported that guggulsterone bound to FXR and NF-κB. Guggulsterone cloud docks into two noncanonical binding sites of FXR, helix 1-loop-helix 2 loop and parts of helix–helix 8 including helix 8-loop-helix 9 [62, 111]. Guggulsterone also binds to the NF-κB precursor protein p105 on its RH domain, which contains sequences important for DNA binding and dimerization, which might be the reason for its NF-κB inhibitory activities [38].

3 Modulation of the Cell Signaling Pathway by Guggulsterone

3.1 *Farnesoid X Receptor*

FXR is a member of the nuclear hormone receptor superfamily and is expressed in the liver, intestine, kidney, adrenals, stomach, fat, and heart [113]. The physiological ligands of FXR are bile acids [58, 71, 99], and it is involved in the regulation of bile acids, cholesterol [69], triglyceride [87], and glucose [114] metabolism. Guggulsterone is a highly efficacious antagonist of FXR, and guggulsterone treatment decreased hepatic cholesterol in wild-type mice fed a high-cholesterol diet but was not effective in FXR-null mice. The inhibition of FXR activation may be the basis for the cholesterol-lowering activity of guggulsterone [97].

In HepG2 cells, in the presence of an FXR agonist such as chenodeoxycholate or GW4064, guggulsterone enhanced endogenous bile salt export pump (BSEP) expression with maximal induction of 400–500 % by the FXR agonist alone. Gugulipid treatment in rats increased expression of BSEP and small heterodimer

partner (SHP) but not cholesterol 7α1 (*Cyp 7α1*), sterol 12α-hydroxylase (*Cyp 8b1*), or intestinal bile acid-binding protein (I-BABP) [17].

FXR may have a role in the development of intestinal metaplasia, which is considered a precursor lesion of cancer in the upper gastrointestinal tract. Guggulsterone induced apoptosis in Barrett's esophagus cells [18] and reduced caudal type homeobox 2 (Cdx2) expression in rat gastric epithelial cells (RGM-1) and in human gut-derived adenocarcinoma cells (Bic-1) [107, 108].

3.2 Other Nuclear Receptors

Nuclear receptors are ligand-modulated transcription factors that bind to DNA and regulate the expression of adjacent genes.

Both E- and Z-guggulsterone displayed high affinity for FXR as well as other steroid receptors, including the androgen, glucocorticoid, and progesterone receptors [8]. Guggulsterone functions as an efficacious constitutive androstane receptor inverse agonist. The ratio of constitutive androstane receptor to PXR determined the activity of guggulsterone against the Cyp2b10 promoter [21].

3.3 Nuclear Factor-κB

NF-κB, a proinflammatory transcription factor, can promote the development of tumors. Various inflammatory agents, carcinogens, tumor promoters, and the tumor microenvironment activate NF-κB. NF-κB proteins themselves and proteins regulated by it have been linked to cellular transformation, proliferation, apoptosis suppression, invasion, angiogenesis, and metastasis. Constitutively activated NF-κB is common in a wide variety of tumors. Furthermore, there exists genetic evidence that NF-κB mediates tumorigenesis. Thus, suppression of NF-κB activation should be effective in the prevention and treatment of cancer [1].

Guggulsterone suppressed DNA binding of NF-κB induced by multistimulation in lung carcinoma cells through inhibition of IκB kinase activation, and it also suppressed induced and constitutive NF-κB activation in most tumor cells. Guggulsterone decreased the expression gene products involved in anti-apoptosis (IAP1, xIAP, Bfl-1/A1, Bcl-2, cFLIP, and survivin), proliferation (cyclin D1 and c-Myc), and metastasis (matrix metalloproteinase [MMP]-9, cyclooxygenase-2 [COX-2], and vascular endothelial growth factor [VEGF]) [82]. These results suggested that guggulsterone suppresses NF-κB and NF-κB-regulated gene products, which many explain its anti-inflammatory and anti-tumor activities.

4 Signal Transducer and Activator of Transcription

Signal transducer and activator of transcription (STAT) 3 is a member of a family of transcription factors. This factor is associated with inflammation, cellular transformation, survival, proliferation, invasion, angiogenesis, and cancer metastasis. Various types of carcinogens, radiation, viruses, growth factors, oncogenes, and inflammatory cytokines have been found to activate STAT3. STAT3 is constitutively active in most tumor cells but not in normal cells [2].

Guggulsterone inhibited angiogenesis by blocking STAT3 and VEGF expression in colon cancer cells (HT-29). It also reduced MMP-2 and MMP-9 enzyme activity in colon cancer cells. The recruitment of STAT3 and anyl hydrocarbon receptor nuclear translocator, but not hypoxia-inducible factor (HIF)-1α, to the VEGF promoter was inhibited by guggulsterone treatment. Human umbilical vein endothelial cells (HUVECs) produced much foreshortened and severely broken tubes and showed decreased migration activity as a result of guggulsterone treatment [43].

Guggulsterone also inhibits interleukin (IL)-6-induced STAT3 activation through the induction of SHP-1 in human multiple myeloma cells (U226). Downregulation of the expression of STAT3-regulated anti-apoptotic (Bcl-2, Bcl-xL, Mcl-1), proliferative (cyclin D1), and angiogenetic (VEGF) gene products occurred in response to guggulsterone treatment; and this correlated with the suppression of proliferation, accumulation of cells in subG1 phase of the cell cycle, and induction of apoptosis [4].

5 Mitogen-Activated Protein Kinase

Mitogen-activated protein kinase (MAPK) pathways are evolutionarily conserved kinase modules that link extracellular signals to the machinery that controls fundamental cellular processes such as growth, proliferation, differentiation, migration, and apoptosis. To date, six distinct groups of MAPKs have been characterized in mammals: extracellular signal-regulated kinase (ERK)1/2, ERK3/4, ERK5, ERK7/8, c-Jun N-terminal kinase (JNK)1/2/3, and the p38 isoforms. Generally, the effect of MAPKs is anti-proliferative and proapoptotic, but dependent on the cellular context they may also contribute to tumorigenesis [20].

Guggulsterone-induced cell death in human prostate cancer cells (PC-3 and LNCaP) was regulated by reactive oxygen intermediate (ROI)-dependent activation of JNK, but independent of ERK1/2 or p38. Guggulsterone did not generate ROIs in normal prostate cancer cells (PrEC) [89], but it inhibited 12-*O*-tetradecanoylphorbol-13-acetate-mediated skin edema and hyperplasia in mice. Treatment with guggulsterone also inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced phosphorylation of ERK1/2, JNK, and p38 [75], and it suppressed the activation of ERK1/2 and JNK in the pancreas of cerulein-induced

murine pancreatitis [41]. MAPKs likely show different responses according to conditions, e.g., stimuli or cell types.

6 PI3K/Akt Signaling

The PI3K-Akt signaling pathway has been firmly established as a critical contributor toward tumorigenesis. This pathway is involved in cell growth, survival, and proliferation within tumors [53].

Guggulsterone-induced apoptosis was related to inactivation of Akt followed by activation of JNK in human monocytic leukemia cells (U937) [85]. Additionally, it inhibited angiogenesis by suppressing the VEGF-VEGF-R2-Akt signaling in HUVECs [101].

7 Inducible Nitric Oxygen Synthase

Nitric oxide (NO) is involved in various physiological functions, and its role in tumorigenesis has been well studied. A large majority of human and experimental tumors appear to progress owing to NO resulting from inducible NO synthase (iNOS), further stimulated by proinflammatory cytokines [33].

Z- and E-guggulsterone were more potent inhibitors of NO production (IC50 = 1.1 and 3.3 μM, respectively) compared with curcumin (IC50 = 12.3 μM) in lipopolysaccharide (LPS)-activated murine macrophages (J774.1) [61]. Guggulsterone prevented cytokines-induced NO correlated with reduced level of iNOS expression in rat insulinoma cells (RINm5F) [54]. It also reduced LPS-induced iNOS mRNA expression in mouse inner medullary collecting duct cells (mIMCD-3) [42].

8 Cyclooxygenase-2

COX-2 converts arachidonic acid to prostaglandins and prostanoids through stimulation. COX-2 has been shown to be one of the key players in the induction of inflammation and tumorigenesis.

Guggulsterone prevented IL-1β-induced and interferon (IFN)-γ-induced COX-2 expression and prostaglandin E2 (PGE2) production in rat insulinoma cells (RINm5F) [54]. It suppressed deoxycholic acid (DCA)-induced and constitutive COX-2 expression and PGE2 production in esophageal adenocarcinoma cells (OE19, OE33) [109].

9 Wnt/Beta (β)-Catenin Signaling

Wnt signaling is involved in virtually every aspect of embryonic development and also controls homeostatic self-renewal in a number of adult tissues. Germline mutations in the Wnt/β-catenin pathway cause several hereditary diseases, and somatic mutations are associated with cancer of the intestine and a variety of other tissues [15].

Guggulsterone reduced β-catenin/T-cell factor 4 complex and Wnt/β-catenin targeting genes, such as cyclin D1, C-myc, and T-cell factor 4 in breast cancer cells (MCF-7, MDA-MB-231), indicating that the β-catenin signaling pathway is the target for gugulipid-induced growth inhibition and apoptosis in human breast cancer [34] (Tables 1 and 2).

10 P-glycoprotein

P-glycoprotein (P-gp) is expressed in many normal human tissues and cancers. P-gp plays a major role in the distribution and excretion of drugs and is involved in the intrinsic and acquired drug resistance of cancers [12]. Targeting the regulation of P-gp and related resistance mechanisms is a potential therapeutic approach against cancer.

Guggulsterone showed a dual inhibitory effect on the function of P-gp and in multidrug-resistant human cells (KB-C2) [65]. When guggulsterone was combined with doxorubicin, it significantly promoted the sensitivity of doxorubicin-resistant human myelogenous leukemia cells (K562/DOX) toward doxorubicin. The inhibitory effect of guggulsterone on P-gp activity was the major cause of increased stagnation of doxorubicin inside K562/DOX cells, indicating that guggulsterone may effectively reverse multidrug resistance in K562/DOX cells via inhibiting the expression and drug transport function of P-gp [105].

11 Role of Guggulsterone in Chronic Diseases

11.1 Hypolipidemic and Anti-adipogenesis Effects

The hypolipidemic effects of guggulsterone have been well established in clinical trials compared with the other bioactivities of guggulsterone. Several animal model studies revealed that guggulsterone attenuates hyperlipidemia in the animals fed a high-fat diet.

Treatment with guggulsterone decreased hepatic cholesterol in wild-type mice fed a high-cholesterol diet but was not effective in FXR-null mice. The inhibition of FXR activation is the basis for the cholesterol-lowering activity of guggulsterone

Table 1 Effects of guggulsterone on diseases other than tumors

Disease	Mechanism/effect	Cells	Animal models
Hypolipidemia	FXR↓, BSEP↑, cholesterol↓ (total, LDL, VLDL), triglyceride↓, HDL↑		FXR-null mice, rats, rabbits, chickens, pigs, monkeys
Diabetes	NO↓, iNOS↓, LI-1β↓, IFNγ↓, COX-2↓, PGE2↓, prevention of β-cell size reduction in high-fat-fed rats, improvement of glucose tolerance in ob/ob mice	RINm5F	Rats, ob/ob mice
Kidney injury	NF-κB↓, iNOS↓, COX-2↓, IL-6↓, TNF-α↓	mIMCD-3	
Drug resistance	P-gp↓, MRP1↓, reversal of doxorubicin resistance	K567/DOX, KB-C2	Xenograft
Obesity	C/EBPs↓, PPATγ↓, FABP↓, SREEBP-1c↓, adipoQ↓, SOCS-3↓ induction caspase-dependent apoptosis in adipocytes	3T3−L1	
Thyroid dysfunction	Increase in iodine uptake by the thyroid		Rats
Cardiovascular disorders	FXR↓, TF↑, PAI-1↓, VCAM-1↓, reversal of metabolic changes, reduction of caspase-dependent apoptosis	H9C2, neonatal rat cardiac myocytes, HAECs	Murine MI/R model
Hepatitis	ICAM-1↓, NF-κB↓, HIF-1α↓, decrease in collagen deposition, hepatic stellate cell apoptosis, blocking upregulated by bile acids, and basal level of hepatic C virus replication	HepG2, LX-2, Huh-7, Hul	Mice
Inflammatory bowel disease	ICAM-1↓, NF-κB↓, IKK↓, IL-2↓, IL-4↓, IFN-γ↓, IL-12↓, TNFα↓	Caco-2, COLO205, BMDC	DSS-, TNBS- or oxazolone-IBD mice, IL-10K/O mice
Pancreatitis	Reduction in pancreas weight/body weight ratio, serum lipase, infiltrations of macrophages and neutrophils		Mice
Arthritis	NF-κB↓, RANTES↓, ENA-78↓, MMP-1↓, MMP-3↓, reversal of thickness and swelling in joints	Fibroblast-like synoviocytes	Rabbits
Neurological disorder	AChe↓, protection of memory deficit, induction of neural stem cells into dopaminergic neurons		Mice
Melanogenesis in skin	Tyrosinase↓, TRP-1↓	B16/10	
Uveitis	NF-κB, ↓NO↓, iNOS↓, COX-2↓, PGE2↓, MMP-2↓	HNPECs	Rats
Respiratory disorder	Reversal of effect by FXR agonist on respiratory rhythm		Rats

↑ indicates upregulation of expression or activation by guggulsterone

↓ indicates downregulation of expression or activation by guggulsterone

[97]. Guggulsterone also showed the ability to enhance the action of agonists of BSEP expression, because gugulipid treatment in rats lowered serum triglyceride and raised high-density lipoprotein (HDL) levels in vivo [17].

Guggulsterone reversed adipogenesis-related gene, CAAT/enhancer-binding protein (C/EBPs), and peroxisome proliferator-activated receptor (PPAR) γ, fatty acid-binding protein, sterol regulatory element binding protein-1c (SREBP-1c), and adipoQ, mRNA expression induced by a FXR ligand in preadipocytes (3T3-L1) [74]. It also induced caspase-dependent apoptosis, reduced the lipid content in adipocytes (3T3-L1), and downregulated the adipocyte-specific transcription factors PPARγ2, C/EBPα, and C/EBPβ [70, 110].

11.2 Diabetes Mellitus

Several studies have implicated guggulsterone is a potential remedy for diabetes. Treatment with guggulsterone prevented IL-1β- and IFN-γ-induced β-cell damage, as well as NO and PGE2 production, and these effects were related to reduced levels of iNOS and COX-2 expression. Guggulsterone prevented cytokines-induced NO and PGE2 production, iNOS and COX-2 expression, Janus kinase/STAT activation, downregulated suppressor of cytokine signaling-3, and impaired glucose-stimulated insulin secretion [54]. It also attenuated the reduction in pancreatic β-cell size, increase in adipocytes, and steatosis of the liver in high-fat-diet-fed rats. Guggulsterone inhibited 3T3-L1 preadipocytes differentiation, and it had both hypoglycemic and hypolipidemic effects that can help to cure type 2 diabetes [80].

Bile acids acutely stimulate insulin secretion by mouse β-cells via FXR activation and K_{ATP} channel inhibition, but guggulsterone suppressed this effect. FXR in pancreatic β-cell may contribute to a pharmaceutical strategy for the treatment of type 2 diabetes mellitus [24]. Furthermore, gugulipid (20 g/kg diet) improved glucose tolerance in female Lep(ob)/Lep(ob) mice [16].

11.3 Thyroid Stimulatory Effects

Guggulsterone showed a strong thyroid stimulatory action, but not through pituitary activation, in rats [94, 95].

11.4 Cardiovascular Protection

Several studies have reported cardioprotective effects of guggulsterone both in vitro and in vivo.

Table 2 Effects of guggulsterone on tumors

Disease/condition	Mechanism/effect	Cells	Animal models
Leukemia	NF-κB↓, COX-2↓, MMP-9↓, cyclinD1↓, Akt↑, JNK↓, cyclinD1↓, cdc2↓, Bfl-1↓, cFLIP↓, Bcl-XL↓, Bcl-2↓, xIAP↓, cMcl1↓, survivin↓, c-Myc↓, caspase-dependent apoptosis	U937	
Head and neck cancer	STAT3↓, HIF-1α↓, NF-κB↓, COX-2↓, VEGF↓, PP2A↑, 14-3-3ζ↓, Bad↓, Bcl-2↓, xIAP↓, cMcl1↓, survivin↓, cyclin D1↓, c-Myc↓, caspase-dependent apoptosis, reduction of tumor xenograft size, enhancing chemotherapy effect	1482, UM-22A, UM-22B, SCC4, HSC2,	Xenograft
Breast cancer	NF-κB↓, AP-1↓, β-catenin↓, cyclinD1↓, c-Myc↓ TCF-4↓, HO-1↑, Nrf2↑, VEGFR2↑	MCF-7, MDA-MB-231, MCF10A	
Lung cancer	NF-κB↓, COX-2↓, MMP-9↓, VEGF↓, cyclinD1↓, IAP1↓, XIAP↓, Bfl-1/A1↓, Bcl-2↓, TRAF1↓, cFLIP↓, survivin↓, induction of apoptosis	H1299	
Intestinal metaplasia	Cdx2↓, MUC-2↓	CP-18821, RGM-1, Bic-1, OE19, OE33,	
Esophageal adenocarcinoma	COX-2↓, PGE2↓, IBABP↓, SHP↓, IL-8↓, MIP3α↓, caspase-dependent apoptosis, reduction of tumor xenograft size	OE19, OE33, TE-7	Xenograft
Colorectal cancer	STAT3↓, VEGF↓, ARNT↓, MMP-2↓, MMP-9↓, caspase-dependent apoptosis, reduction of tumor xenograft size	HT-29	Xenograft
Pancreatobiliary cancer	FXR↓, SrC↓, Jak/STAT↓, MUC4↓, JNK↓, NF-κBp65↓VEGF-c↓, MMP-2↓, enhancement of chemotherapy effect	MIA-PaCa2, PANC-1, CD18/HPAF, Capan1, TGBC1, TGBC2	Xenograft
Hepatoma	Sensitization to TRAIL	Hep3B, HepG2	
Prostate cancer	ROI↑, JNK↓, ACLY/Akt↓, reduction of tumor xenograft size	PC-3, LNCaP, PrEC	Xenograft
Brain tumor	Ras↓, NF-κB↓, sensitization to SANT-1	A172, U87MG, T98G	
Bone metastasis	NF-κB↓, RANKL↓, RUNX2↓, interference with osteoblastic differentiation, prevention of migration	MDA-MB-468, U226, BMSC, MG63	
Radiosensitivity	NF-κB↓, IGF-Rα↓, ERα↓, inhibition of DNA double-strand break repair	PC-Sw, MFC-7, HT-29	
Drug resistance	P-gp↓, MRP1↓, reversal of doxorubicin resistance	MCF-7/DOX, KB-C2	Xenograft

↑ indicates upregulation of expression or activation by guggulsterone

↓ indicates downregulation of expression or activation by guggulsterone

A marked protective effect was shown by guggulsterone on cardiac enzymes and the P450 system against myocardial necrosis induced by isoproterenol in rats [37]. Guggulsterone showed marked reversal of the metabolic change in the heart, with increased phospholipase, decreased cardiac glycogen, and increased cytosolic lipid peroxide, related to ischemia of the heart induced by isoproterenol in rats [10].

Guggulsterone reduced DOX-induced apoptosis and cell death in cardiomyocytes (H9C2). Pretreatment using guggulsterone reversed DOX-induced decreases in PARP, caspase-3, and bcl-2 and increases in Bax, cytochrome C release, cleaved-PERP, and cleaved caspase-3 [100].

siRNA-mediated silencing of endogenous FXR or guggulsterone reduced post-ischemic myocardial apoptosis in murine myocardial ischemia. FXR acted as a novel functional receptor in cardiac tissue, regulated apoptosis in cardiomyocytes, and contributed to myocardial ischemia/reperfusion injury [72].

Guggulsterone inhibited TNF-α-induced endothelial tissue factor protein and mRNA expression and surface activity in human aortic endothelial cells. It enhanced endothelial tissue factor pathway inhibitor and impaired plasminogen activator inhibitor-1 as well as vascular cell adhesion molecule-1 (VCAM-1) protein. Guggulsterone offers a novel therapeutic option, in particular in inflammatory disease associated with an increased risk of thrombosis [26].

11.5 Hepatoprotective Effects

Treatment with guggulsterone inhibited intracellular adhesion molecule-1 expression by GW4064, a FXR selective agonist, in human hepatocytes (HepG2) [73]. Guggulsterone attenuated activation and survival of hepatic stellate cells (LX-2) by inhibiting NF-κB activation and inducing apoptosis. High-dose guggulsterone decreased the extent of collagen deposition and the percentage of activated hepatic stellate cells undergoing apoptosis in mice [40]. HIF-1α expression was also reduced by guggulsterone in hypoxic conditions in hepatocytes (HepG2) [64].

The bile acid-mediated increase in HCV RNA in hepatocytes (Huh-7, GS4.1) was reduced by guggulsterone [11], and it blocked upregulation by bile acids and basal levels of hepatic C virus replication in an HCV replication model (Hul cells) [79].

11.6 Kidney Protection Effects

LPS treatment of mouse inner medullary collecting cells produced pro-inflammatory molecules such as iNOS, COX-2, IL-6, and TNF-α; however, guggulsterone treatment inhibited this process. Guggulsterone inhibited the degradation of Iκ-Bα and translocation of NF-κB and could inhibit inflammatory responses in

collecting duct cells, which may contribute to kidney injury due to systemic infection [42].

11.7 Inflammatory Bowel Disease

Several in vitro and in vivo studies implicated guggulsterone as an attractive therapeutic option in the treatment of inflammatory bowel disease.

Guggulsterone significantly inhibited LPS- or IL-1β-induced intracellular adhesion molecule-1 gene expression, NF-κB transcriptional activity, IκB phosphorylation/degradation, and NF-κB DNA binding activity in colon cancer cells (Caco-2) or rat intra-epithelial cells (IEC-18). Moreover, guggulsterone strongly blocked IKK activity [13] and attenuated the generation of IL-2 and IL-4 and IFN-γ as well as T-cell proliferation (Mencarel[52].

GG-52, a guggulsterone derivative, blocked NF-κB activation in colon cancer cells (COLO 205) [44], and LPS-induced IL-12p40 and TNF-α gene expression, IκBα degradation, and NF-κB DNA binding activity in bone marrow-derived dendritic cells [44].

Both guggulsterone and GG-52 have also been reported to attenuate different murine inflammatory bowel disease models in vivo [13, 36, 44, 60].

11.8 Pancreatitis

Pre-treatment with guggulsterone attenuated histological damage, reduced pancreas weight/body weight ratio, decreased serum lipase levels, inhibited infiltration of macrophages and neutrophils, and suppressed cytokine production in murine cerulei-induced acute pancreatitis [41].

11.9 Arthritis

Guggulsterone blocked IL-1β-mediated inflammatory proteins, such as regulated in activation normal T-cell expressed and secreted, epithelial neutrophil activating peptide-78, MMP-1 and MMP-3 by suppressing NF-κB activation in fibroblast-like synoviocytes [50].

Guggul decreased the thickness of joint swelling in an experimental rabbit arthritis model resembling rheumatoid arthritis in humans [81].

In a human study, 30 male and female participants with arthritis received gum guggul. Participants showed significantly improved Western Ontario and MacMaster Osteoarthritis Index total scores after taking the supplement for

1 month and continued to improve at the 2-month time point and during follow-up [88].

11.10 Neuroprotective Effects

Gugulipid (p.o.) treatment showed improvements in scopolamine-induced deficits in a passive avoidance test in mice. Gugulipid (i.c.) treatment had protective effects in a streptozotocin-induced memory deficit model of dementia that can be attributed to antioxidant and anti-acetylcholinesterase (AChE) activities of gugulipid. These observations suggested gugulipid as a potential anti-dementia drug [78].

In addition, guggulsterone was found to be highly effective. These neurons have been extensively characterized and shown to be functional. This new approach may offer a practical route to creating neurons of sufficient quality to be used to treat Parkinson's disease [28].

11.11 Nodulocystic Acne

Treatment with gugulipid (50 mg guggulsterone) for 3 months resulted in a 68 % decrease inflammatory lesions in patients with nodulocystic acne. Patients with oily faces responded remarkably to gugulipid [93].

11.12 Melanogenesis in Skin

Treatment with guggulsterone dose dependently inhibited isobutylmethylxanthine-induced melanogenesis and cellular tyrosinase activity with no cytotoxicity in melanoma cells (B16/F10). Decreased melanin biosynthesis was accompanied by the reduced expression of melanogenesis-related genes, such as tyrosinase, microphthalmia-associated transcription factor, tyrosinase-related protein (TRP)-1, and TRP-2 [45].

11.13 Uveitis

Guggulsterone prevented the expression of endotoxin-induced uveitis (EIU)-induced inflammatory markers, such as MMP-2, NO, and PGE2 in rats. It also prevented the expression of MMP-2, iNOS, and COX-2 proteins and of IκB and NF-κB in various eye tissues of rats. Treatment with guggulsterone inhibited LPS-induced expression of inflammatory proteins in human primary nonpigment

ciliary epithelial cells. Guggulsterone could be a novel option for the treatment of ocular inflammation [35].

11.14 Respiratory Diseases

FXR agonists are able to regulate respiratory rhythm, and guggulsterone completely reversed the effect of FXR agonists in neonatal rat brainstem medulla oblongata slices. FXR is a potential therapeutic target in treating respiratory diseases [115].

11.15 Anti-tumor

Treatment with guggulsterone suppressed DNA binding of NF-κB induced by multistimulation in lung carcinoma cells (H1299) through inhibition of IκB kinase activation. Guggulsterone suppressed induced and constitutive NF-κB activation in most tumor cells (A549, KBM-5, Jurkat, U266, MDA1986). Guggulsterone decreased the expression of gene products involved in anti-apoptosis (IAP1, xIAP, Bfl-1/A1, Bcl-2, cFLIP, and survivin), proliferation (cyclin D1 and c-Myc), and metastasis (MMP-9, COX-2, and VEGF) [82, 85].

Guggulsterone inhibited angiogenesis by blocking STAT3 and VEGF expression, which play important roles in angiogenesis, in colon cancer cells (HT-29) and neck squamous cell carcinoma cells (SCC4, HSC2) [43, 56].

Therefore, guggulsterone is considered as a promising option for chemoprevention as well as therapy against tumors.

11.16 Leukemia

Guggulsterone inhibited the proliferation of human leukemia cells (U937, jurkat, KBM-5, and K562). It induced S-phase arrest correlated with a decrease in cyclin D1 and cdc2, and induced caspase-dependent apoptosis through activation of JNK and suppression of the Akt pathway in leukemia cells (U937). [82].

11.17 Head and Neck Cancer

The effect of bortezomib to induce cell death through STAT3 inhibition was enhanced by guggulsterone in neck squamous cell carcinoma cells (PCI-37a, UM-22b, and 1483) [51].

Guggulsterone induced apoptosis and cell cycle arrest, inhibited invasion, and enhanced the efficacy of erlotinib, cetuximab, and cisplatin in human head and neck squamous cell carcinoma cells (HNSCCs) (1483, UM-22A, and UM-22B). It decreased total and phosphotyrosine STAT3 as well as HIF-1α in HNSCCs. In a xenograft model of HNSCCs, guggulsterone treatment increased apoptosis and decreased expression of STAT3. Guggulsterone-mediated inhibition of STAT3 and HIF-1α provided a biologic rationale for further clinical investigation in the treatment of HNSCCs [52]. Treatment with guggulsterone in HNSCCs (SCC4, HSC2) abrogated both smokeless tobacco- and nicotine-induced nuclear activation of NF-κB and pSTAT3 proteins and their downstream targets COX-2 and VEGF. Guggulsterone treatment decreased the level of ST- and nicotine-induced secreted interleukin-6 in culture media of HNSCCs [56].

Treatment with guggulsterone released Bad from the inhibitory action of 14-3-3 ζ(zeta) in proliferating SCC4 cells by activating protein phosphatase 2A (PP2A). These events initiated the intrinsic mitochondrial pathway of apoptosis. Guggulsterone treatment reduced the expression of anti-apoptotic proteins, Bcl-2, xIAP, Mcl1, survivin, cyclin D1, and c-Myc, thus committing cells to apoptosis. These events were followed by activation of caspase-9, caspase-8, and caspase-3. 14-3-zeta, a multifunctional phospho-serine/phospho-threonine binding protein, was a molecular target in guggulsterone-induced apoptosis in head and neck cancer cells (SCC4) [55].

11.18 Breast Cancer

E- and Z-guggulsterone downregulated MMP-9 expression and tumor invasion through the IKK/NF-κB pathway and MAPK/activator protein-1, respectively, in breast cancer cells (MCF-7). A combination of these isomers exerted an additive effect in the inhibition of cell invasion [66].

E-guggulsterone induced heme oxygenase-1 expression through inhibition of AKT phosphorylation and NF-E2-related factor 2 activation in human mammary cells (MCF10A) [5].

Deoxycholate promoted the expression of vascular endothelial growth factor receptor 2 (VEGFR2) and decreased ceramide-mediated apoptosis of breast cancer progenitor cells (4T1). Guggulsterone reduced VEGFR2 expression and angiogenesis in endothelial cell culture [46].

Z-guggulsterone reduced β-catenin/TCF-4 complex and Wnt/β-catenin targeting genes, such as cyclin D1, c-Myc, and TCF-4, in breast cancer cells, indicating that β-catenin signaling pathway is the target for gugulipid-induced growth inhibition and apoptosis in human breast cancer (MCF-7, MDA-MB-231) [34].

11.19 Lung Cancer

Guggulsterone has been also reported to suppress NF-κB activation induced by tumor necrosis factor (TNF), phorbol ester, okadaic acid, cigarette smoke condensate, hydrogen peroxide or IL-1 through inhibition of IκB degradation in non-small lung cancer cells (H1299). Guggulsterone also suppressed COX-2, MMP-9, VEGF, and cyclin D1 expression, as well as inhibiting proliferation and inducing apoptosis [82].

11.20 Intestinal Metaplasia

The effects of chenodeoxycholic acid and GW4064, an FXR antagonist, on mRNA expression of Cdc2 and goblet-specific gene mucin 2 were abolished by guggulsterone in normal rat gastric epithelial cells (RGM-1) [107].

11.21 Esophageal Cancer

FXR was significantly overexpressed in Barrett's esophagus compared with normal mucosa, esophagitis, and esophageal adenocarcinoma. Guggulsterone induced apoptosis and caspase-3 activity in Barrett's esophagus-derived cells (CP-18821) [18]. Expression of FXR, the bile acid metabolism genes I-BABP and SHP, and the chemokines IL-8 and macrophage inflammatory protein 3α were increased in Barrett's epithelium. DCA induced FXR, I-BABP, macrophage inflammatory protein 3α, and IL-8 mRNA expression in an esophageal cell line (TE7), and guggulsterone abolished DCA-induced mRNA expression [9]. Inhibition of FXR by FXR shRNA or guggulsterone suppressed esophageal cancer cell viability and induced apoptosis in vitro and reduced tumor formation and growth in nude mouse xenografts in vivo [30].

Guggulsterone suppressed DCA-induced and NF-κB-dependent activation of Cdx2 and COX-2 expression. Furthermore, guggulsterone also reduced the viability of esophageal adenocarcinoma cells. Guggulsterone may serve as candidate for preventing and treating esophageal adenocarcinoma as well as Barrett's esophagus [109].

11.22 Colorectal Cancer

Treatment with guggulsterone significantly increased apoptosis in colon cancer cells (HT-29) by activating caspase-3 and caspase-8. The size of tumors in

guggulsterone-treated mice was significantly smaller than the size of tumors in control mice [6]. Guggulsterone also inhibited angiogenesis by blocking STAT3 and VEGF expression, and reducing MMP-2 and MMP-9 enzyme activity in HT-29 cells [43].

Thus, there is a potential therapeutic use for guggulsterone in the treatment of colorectal cancer.

11.23 Pancreatobiliary Cancer

FXR overexpression in pancreatic cancer tissue with lymph node metastasis is associated with poor patient survival. siRNA-mediated downregulation of FXR and guggulsterone-mediated FXR inhibition resulted in marked reduction in cell migration and invasion human pancreatic cells (MIA-PaCa2, PANC-1) [49]. Guggulsterone inhibited proliferation, decreased motility and invasion, and induced apoptosis in pancreatic cancer cells (CD18/HPAF, Capan1). These anti-tumor effects of guggulsterone possibly involve multiple networks including inhibition of Src and Jak/STAT signaling, alteration in Bad phosphorylation, recognition of actin cytoskeleton, and down-regulation of MUC4, which is involved in chemoresistance [57].

In vitro, the combination treatment of guggulsterone with gemcitabine resulted in more growth inhibition and apoptosis through the downregulation of NFκ-B activity with Akt and Bcl-2 and through the activation of JNK and Bax in pancreatic cancer cells. In vivo, combination therapy amended tumor growth inhibition through the same mechanism as in tumor tissue. The combination therapy with guggulsterone and gemcitabine has the potential to become a valuable strategy for the treatment of pancreatic cancer [3].

Guggulsterone inhibited the proliferation and suppressed migration and invasion of gallbladder cancer cells (TGBC1, TGBC2), and it decreased NF-κB p65, VEGF-C, and MMP-2 activities. Gallbladder cancer cells treated with a combination of guggulsterone and gemcitabine demonstrated inhibition of cell proliferation and invasion compared with treatment with gemcitabine alone. Guggulsterone could be a potential therapeutic option for patients with gallbladder cancer [112].

11.24 Hepatoma

Death receptor DR5 induction via eukaryotic initiation factor-2α and C/EBF homologous transcription factor was crucial for the marked synergetic effects induced by TNF-related apoptosis including ligand and guggulsterone in human hepatocellular carcinoma cells (Hep3B, HepG). Guggulsterone- /TNF-related apoptosis, including ligand combination, could represent a novel tool for cancer therapy [63].

11.25 Prostate Cancer

Guggulsterone induced caspase-dependent apoptosis in part mediated by Bax and Bak in prostate cancer cells (PC-3) [90]. Guggulsterone-induced cell death in human prostate cancer cells (PC-3 and LNCaP) was regulated by ROI-dependent activation of JNK but not in normal prostate cancer cells (PrEC) [89]. Gugulipid-induced apoptosis was associated with ROS production and was regulated by JNK signaling axis in human prostate cancer cells. Representative normal prostate epithelial cells (PrEC) were relatively more resistant to gugulipid-mediated cellular responses compared with prostate cancer cells [102]. Guggulsterone inhibited prostate cancer growth also via inactivation of Akt regulation by ATP citrate lyase signaling in human prostate cancer cells (PC-3 and LNCaP) [25].

11.26 Brain Tumors

Although the sonic hedgehog pathway effector Gli1 is overexpressed in gliomas, a sonic hedgehog inhibitor, SANT-1, failed to induce apoptosis in glioblastoma cells (A172, U87MG, T98G). However, guggulsterone inhibited Ras and NF-κB activity and sensitized glioblastoma cells to SANT-1-induced apoptosis [22].

11.27 Bone Metastasis

Receptor activator of NF-κB ligand (RANKL), a member of the TNF superfamily, was implicated as a major mediator of bone resorption, suggesting that agents that can suppress RANKL signaling have the potential to inhibit bone resorption or osteoclastogenesis. Guggulsterone suppressed RANKL-activated NFκ-B activation and differentiation of monocytes into osteoclasts. Guggulsterone completely suppressed differentiation of monocytes into osteoclasts induced by co-incubation of human breast tumor cells (MDA-MB-468) or human multiple myeloma cells (U266). Guggulsterone suppressed RANKL and tumor cell-induced osteoclastogenesis by suppressing the activation of NF-κB [31]. Chenodeoxycholic acid stimulated the expression osteoblast marker genes (bone sialoprotein, osteocalcin, osteopontin, and alkaline phosphatase), as well as DNA binding activity of the bone transcription factor RUNX2 in human bone marrow stromal cells (BMSCs). Guggulsterone inhibited alkaline phosphatase activity, calcium deposition, DNA binding RUNX2, and bone marker expression, indicating that guggulsterone interfered with osteoblastic differentiation [32].

Deoxycholate released from human osteoblast-like MG63 cells or bone tissue promoted cell survival and induced the migration of metastatic human breast cancer

cells (MDA-MA-231). Guggulsterone prevented the migration of these cells and induced apoptosis [86].

11.28 Radiosensitivity

Radiation-induced NF-κB activation was inhibited by guggulsterone and this enhanced radiosensitivity in pancreatic cells (PC-Sw), and it reduced both cell cycle movement and growth. Guggulsterone reduced ERα protein levels in breast cancer cells (MFC-7) and insulin-like growth factor receptor β-protein in colon cancer cells (HT-29) and pancreatic cancer cells (PC-Sw) and inhibited DNA double-strand break repair following radiation. The ability of guggulsterone to modulate radiosensitivity in human cancer cell lines needs further study [14].

11.29 Drug Resistance

Co-administration of guggulsterone (10 μM) resulted increases the chemosensitivity of MCF-7/DOX cells to doxorubicin, compared with doxorubicin treatment alone [103]. When doxorubicin and guggulsterone were co-administered, their anti-tumor activities were augmented in MCF-7/DOX xenografts. Examining body weight, hematological parameters, hepatic cardiac, and gastrointestinal tract histopathology revealed that no significant signs of toxicity were related to guggulsterone. Guggulsterone might reverse doxorubicin resistance in vivo, without severe side effect [104].

Co-administration of guggulsterone increased chemosensitivity of imatinib-resistant K562 cells (K562/IMA) to imatinib compared with imatinib treatment alone. Guggulsterone induced apoptosis by inhibiting COX-2 and PGE2 and downregulating P-gp expression [106].

12 Biological Activities of Guggulsterone in Animal Models

12.1 Hypolipidemic Effects

A primary study reported that administration of gum guggul lowered serum cholesterol levels in hypercholesterolemic rabbits. Hypercholesterolemia was induced in male albino rabbits by the administration of cholesterol (500 mg/kg body weight). The experimental group was fed gum guggul 2 g/kg body weight daily for 6 weeks. In both the control and experimental cholesterol treated groups,

an increase in serum and tissue cholesterol level was observed; however, the gum guggul-treated group exhibited significantly lower serum and liver cholesterol levels. In this study, a significant decrease in the body weight of the rabbits fed gum guggul was observed [77]. However, an effect of guggul on triglyceride was not shown in this study.

Another experiment showed that treatment with guggulsterone (25 mg/kg body weight for 10 days) resulted in a 27 % decrease of serum cholesterol and a 31 % decrease in serum triglyceride levels in rats. In the same study, membranes prepared from the livers of guggulsterone-treated rats exhibited up to an 87 % increase in binding sites [91]. Guggulsterone treatment improved fasting blood glucose, glucose tolerance, plasma insulin level, level of harmful lipid (total, low-density lipoprotein [LDL], very low-density lipoprotein [VLDL] cholesterol, and triglyceride), expression profiles of various genes involved in lipid metabolism in high-fat-diet-fed mice [80]. The hypolipidemic effect of guggul has been reported in several other animal models, including chicken [7], Indian domestic pig [39], Presbytis monkey [23], and albino rat [48].

Guggulsterone treatment decreased hepatic cholesterol in wild-type mice fed a high-cholesterol diet but was not effective in FXR-null mice. The inhibition of FXR activation is the basis for the cholesterol-lowering activity of guggulsterone [97].

Gugulipid treatment in rats lowered serum triglyceride and increased HDL levels. Guggulsterone is considered as a novel class of FXR ligand characterized by antagonist activities in coactivator association assays but with the ability to enhance the action of agonists on BSEP expression in vivo (Fisher rats) [17].

12.2 Diabetes Mellitus

Treatment with guggulsterone improved fasting blood glucose, glucose tolerance, plasma insulin level, level of harmful lipids, expression profiles of various genes involved in carbohydrate, and lipid metabolism (phosphoenol pyruvate carboxykinase, glucose-6-phosphatase, glucose transporter-4, PPARγ, and TNF-α) in high-fat-diet-fed mice. Guggulsterone also attenuated reductions in pancreatic β-cell size, increases in adipocytes, steatosis of the liver in high-fat-diet-fed mice. Guggulsterone had both hypoglycemic and hypolipidemic effects that can help to treat type 2 diabetes [80]. In addition, gugulipid (20 g/kg diet) improved glucose tolerance in female Lep(ob)/Lep(ob) mice [16].

12.3 Thyroid Stimulatory Effects

Guggulsterone showed a strong thyroid stimulatory action when administered to albino rats. Its administration (1 mg/100 g body weight) brought about an increase in iodine uptake by the thyroid and enhanced activities by thyroid peroxidase and

protease as well as oxygen consumption by isolated slices of liver and biceps muscle [94]. The thyroid was not stimulated by guggulsterone through pituitary activation in rats pretreated with carbimazole (10 mg/kg body weight) [95].

12.4 Cardiovascular Protection

Treatment with guggulsterone (50 mg/kg body weight orally [p.o.] for 5 days) showed a marked protective effect on cardiac enzymes and the P450 system against myocardial necrosis induced by isoproterenol in rats [37]. Treatment with both isomers of guggulsterone (50 mg/kg body weight p.o.) protected against cardiac damage induced by isoproterenol as assessed by the reversal of blood and heart biochemical parameters in rats [10].

Commiphora mukul (100, 200 and 400 mg/kg body weight p.o. for 30 days) was administered. On the 29th and 30th days, animals in the isoprenaline control and *Commiphora mukul* pretreatment groups were administered isoprenaline (85 mg/kg subcutaneously [s.c.]), consecutively at an interval of 24 h. *Commiphora mukul* pretreatment reversed the isoprenaline-induced oxidative changes in the rat myocardium. Furthermore, histopathological examination showed a reduction in necrosis, edema, and inflammation after *Commiphora mukul* pretreatment [68].

Guggulsterone or siRNA-mediated silencing of endogenous FXR reduced post-ischemic myocardial apoptosis in a murine model of myocardial ischemia/reperfusion injury [72].

In addition, guggulsterone inhibited tissue factor activity and photochemical injury induced by thrombotic occlusion of the carotid artery in mice. These findings indicated that guggulsterone may be a novel therapeutic option for the prevention of thrombosis [26].

13 Hepatoprotective Effects

High-dose guggulsterone (50 mg/kg in 5 % dextrose [0.1 ml] by gavage 5 days per week for 5 weeks) decreased the extent of collagen deposition and the percentage of activated hepatic stellate cells undergoing apoptosis in liver fibrosis model mice (thioacetamine 200 mg/kg body weight 3 times per week for 6 weeks). This suggests that guggulsterone may be useful as an antifibrotic agent in chronic liver diseases [40].

13.1 Inflammatory Bowel Disease

Several animal studies have been reported to show the potential of guggulsterone as a therapeutic option for inflammatory bowel disease.

Administration of guggulsterone significantly reduced the severity of dextran sulfate sodium (DSS)-induced murine colitis as assessed by clinical disease activity score, colon length, and histology. Furthermore, tissue upregulation of IκB and IKK phosphorylation induced by DSS was attenuated in guggulsterone-treated mice [13].

E-guggulsterone effectively attenuated the severity of wasting disease, fecal score, and colon inflammation in murine colitis induced by trinitro-benzene sulfonic acid and oxazolone [52].

In addition, GG-52 blocked and attenuated DSS-induced acute murine colitis and in an IL-$10^{-/-}$ mouse model chronic colitis [36, 44]. Both GG-52 and guggulsterone are potential therapeutic agents for inflammatory bowel disease.

13.2 Pancreatitis

In an analysis of pancreatitis, guggulsterone was administered (10, 25, or 50 mg/kg body weight intraperitoneal [i.p.]) 1 h before the first cerulein treatment (50 mg/kg body weight i.p. hourly for 6 h). Mice were sacrificed 6 h after the final cerulein injection. Pretreatment with guggulsterone attenuated cerulein-induced histological damage, reduced pancreas weight/body weight ratio, decreased serum lipase levels, inhibited infiltrations of macrophages and neutrophils, and suppressed cytokine production. In addition, guggulsterone treatment suppressed the activation of ERK and JNK in the pancreas in cerulein-induced pancreatitis. In conclusion, our results suggested that guggulsterone could attenuate pancreatitis via inactivation of ERK and JNK [41].

13.3 Arthritis

Guggul administration (500 mg/kg body weight daily p.o. for 5 months) decreased the thickness of the joint swelling during the course of drug treatment. These results indicated the beneficial role of guggul in experimental rabbit arthritis resembling rheumatoid arthritis in humans [81].

13.4 Neuroprotective Effects

Gugulipid (12.5, 25, and 50 mg/kg, p.o.) showed dose-dependent improvements in scopolamine-induced deficits in a passive avoidance test. Intracerebral (i.c.) injections of streptozotocin (0.5 mg/kg, 1st and 3rd day) caused murine dementia. Pre- and post-treatment against streptozotocin (i.c.) with gugulipid (50 mg/kg, p.o.) significantly attenuated memory deficit and dementia activity, respectively. Gugulipid treatment caused significant decreases in AChE activity compared with vehicle administration in streptozotocin (i.c.)-treated mice. The study demonstrated that gugulipid had a significant protective affect against streptozotocin-induced memory deficits in a model of dementia that can be attributed to the antioxidant and anti-AChE activity of gugulipid. These observations suggested gugulipid as a potential anti-dementia drug [78].

13.5 Uveitis

EIU was induced by subcutaneous injection of LPS (150 mg) into rats treated with guggulsterone (30 mg/kg body weight i.p.) or control. After 24 h, the rats were sacrificed, eyes were enucleated, and aqueous humor was collected. The expression levels of MMP-2, iNOS, COX-2, phospho-IκB, and phospho-NF-κB were determined immunohistochemically. Compared with the control, the EIU rat eye aqueous humor had a significantly higher number of infiltrating cells and inflammatory markers, such as MMP-2, NO, and PGE2, and treatment with guggulsterone prevented EIU-induced increases. Guggulsterone also prevented the expression of MMP-2, iNOS, and COX-2 proteins and of IκB and NF-κB in various eye tissues. These results suggested that the supplementation of guggulsterone could be a novel approach for the treatment of ocular inflammation [35].

13.6 Anticancer Effects

In a xenograft model of HNSCCs, guggulsterone treatment resulted in increased apoptosis and decreased expression of STAT3. In vivo treatment with gugulipid resulted in decreased rates of tumor growth and enhancement of cetuximab activity [51].

Gastroesophageal reflux is a risk factor for esophageal adenocarcinoma, and bile acids and their receptor, FXR, have been implicated in esophageal tumorigenesis. Inhibition of FXR by FXR shRNA or guggulsterone suppressed esophageal cancer cell (SKGT-4) viability and induced apoptosis in vitro and reduced tumor formation and growth in nude mouse xenografts [30].

Guggulsterone reduced the size of colon cancer cell (HT-29) xenograft tumors in guggulsterone-treated mice more than tumors in control mice [6].

The combination of guggulsterone with gemcitabine enhanced antitumor efficacy through apoptosis in a pancreatic cancer cell (MiaPaCa-2) xenograft model using nude mice [3].

Oral gavage of guggulsterone significantly retarded the growth of prostate cancer cell (PC-3) xenografts in athymic mice without causing weight loss or any other side effects. The guggulsterone-induced apoptosis was associated with downregulation of ATP citrate lyase/Akt signaling [25].

When doxorubicin and guggulsterone were co-administrated, their antitumor activities were augmented in MCF-7/DOX xenografts. Examining body weight, hematological parameters, and hepatic, cardiac, and gastrointestinal tract histopathology revealed that no significant signs of toxicity were related to guggulsterone. Guggulsterone might reverse doxorubicin resistance in vivo with no severe side effects [104].

14 Biological Activities of Guggulsterone in Humans

14.1 Hypolipidemic Effects

Several clinical trials have been conducted to evaluate the hypolipidemic effect of gum guggul, gugulipid, ethyl acetate extract, ether soluble fraction of guggul and guggulsterone. Although most of these studies have shown that guggul lowers serum cholesterol and triglycerides, some studies failed to show hypolipidemic effects. These variations in outcomes remain unexplained.

A clinical trial was reported in 1971 that the ether extract (fraction A) of gum guggul (0.5 g daily) was given to 20 patients with elevated lipid levels for 12 weeks. Serum cholesterol, triglyceride, and phospholipid levels were lowered by 27, 29, and 18 %, respectively [59]. In one double-blind randomized controlled study in obese subjects, gum guggul extract (1 g twice daily) was given to obese patients for 3 weeks. The study showed reduced serum lipid levels in hyperlipidemic subjects [47].

Treatment with gum guggul (3 g three times daily) and fraction A (0.5 g daily) for 21 days decreased serum lipid levels in hypercholesterolemic and hyperlipidemic patients but not in obese hyperlipidemic patients. When the study was repeated with obese subjects, guggul extract significantly reduced the serum lipid levels in hyperlipidemic non-obese patients; however, the hypolipidemic effects were not observed in obese subjects [96]. In 13 of 22 patients with hyperlipidemia, administration of gugulipid (0.5 g 3 times daily for 6 weeks) also lowered the serum cholesterol levels by 25 % and serum triglyceride levels by 25 % [29]. Another double-blind randomized controlled study in 10 healthy subjects fed guggulsterone (25 mg daily for 8 weeks) showed a significant decrease in total

serum cholesterol levels [27]. It was found that total cholesterol and triglyceride levels were decreased by 22 and 27 %, respectively, and HDL-cholesterol level was increased by 36 % in 40 patients suffering from hyperlipidemia received gum guggul (4.5 g daily 16 weeks) [98].

In the largest multicenter clinical trial and a double-blind crossover study, the efficacy of gugulipid alongside clofibrate was tested. In total, 205 subjects completed a 12-week open trial receiving gugulipid (0.5 g daily) or placebo following an 8-week diet. Gugulipid reduced serum cholesterol and triglyceride levels in 70–80 % of the subjects. Average reductions in the levels of serum cholesterol and triglycerides with gugulipid treatment were 11 and 16.8 %, respectively. Hypercholesterolemic patients responded better to gugulipid than hypertriglyceridemic patients who responded better to clofibrate therapy. In mixed hyperlipidemic patients, the response to both drugs was similar. HDL level increased in 60 % of cases who responded to gugulipid therapy; however, clofibrate had no effect on HDL [96]. The first study was published in Western medical literature. In another randomized, double-blind study, 61 patients with hypercholesterolemia divided into two groups received either gugulipid (50 mg twice daily) or placebo for 24 weeks after a low-fat diet with fruits and vegetables for 12 weeks prior to the treatment. Treatment with gugulipid decreased total cholesterol levels by 11.7 %, LDL by 12.5 %, triglycerides by 12.0 %, and total cholesterol/HDL ratio by 11.1 % from the post-diet levels, whereas the levels were unchanged in the placebo group. HDL-cholesterol levels showed no changes in the two groups. After a 12-week washout period, subjects treated with gugulipid exhibited substantial increases in total cholesterol by 6.5 %, LDL by 6.6 %, and triglyceride by 7.7 %, whereas such increases were not observed in the placebo group [96].

The first clinical trial in the USA, a double-blind, randomized, placebo-controlled trial, was carried out with 103 healthy adults with hypercholesterolemia to evaluate the short-term efficacy of gugulipid in a Western population. The subjects received an oral dose of 1 g or 2 g gugulipid or placebo 3 times daily for 8 weeks. The study reported no significant changes in the levels of total serum cholesterol, HDL, VLDL, or triglyceride following the treatment. In this study, only 18 % of subjects showed a 5 % decrease in LDL. In total, 45 subjects with high baseline LDL levels who received 2 g or 1 g gugulipid showed 14 and 10 % reductions in serum triglyceride, respectively [92]. The double-blind, randomized, placebo-controlled study in Norwegian subjects was carried out to evaluate the efficacy of guggul extract on healthy adults with moderately increased cholesterol. Thirty-four subjects randomized into two groups received 2160 mg guggul or placebo for 12 weeks. After 12 weeks, mean levels of total cholesterol and HDL in the active-treatment group were reduced compared with the placebo group. However, the mean levels of LDL, triglycerides, and total cholesterol/HDL ratio between the two groups did not change significantly [67].

The differences in study outcomes may be attributed to differences in ethnic and genetic backgrounds, dietary habits, lifestyle, and the kinds of guggul extract examined.

14.2 Arthritis

Thirty male and female participants with arthritis were administered gum guggul in capsule form (500 mg concentrated) along with food. On the primary measure, the Western Ontario and MacMaster Osteoarthritis Index total score, participants showed significant improvement ($p < 0.0001$) after taking the supplement for 1 month and continued to improve at the 2-month marker and follow-up. There were no side effects reported during the trial. Gum guggul appeared to be a relatively safe and effective supplement to reduce the symptoms of osteoarthritis [88].

14.3 Nodulocystic Acne

Twenty patients with nodulocystic acne were randomly allocated to one of two treatment schedules tetracycline (500 mg) or gugulipid (equivalent to 25 mg guggulsterone). Both were taken twice daily for 3 months, and gugulipid and tetracycline reduced inflammatory lesions by 65.2 and 68 %, respectively; this difference was not statistically significant ($p > 0.05$). Follow-up at 3 months showed a relapse in 4 cases on tetracycline and 2 cases on gugulipid. An interesting observation was that the patients with oily faces responded remarkably better to gugulipid [93].

15 Conclusion

According to the indications of guggul for various disorders in the ancient Ayurveda and the recent accumulation of data provided by in vitro experiments, guggulsterone seems to have multiple pharmacological activities, especially hypolipidemic, anti-inflammatory, and anti-tumor effects. Although some animal models and clinical trials showed the hypolipidemic effects of guggulsterone, other clinical studies did not confirm these hypolipidemic effects. The variations among results of these clinical trials could be attributed to the differences in study design, sample size, subject population, dose, and the kind of guggul extract. Larger and well-designed clinical studies are necessary to demonstrate the efficacy of guggulsterone in hypolipidemic therapy as well as to find a biomarker for the selection of guggulsterone therapy responders.

In contrast to a certain amount of clinical trials on its hypolipidemic effect, there have been few clinical trials in anti-inflammation or anti-tumor effects of guggulsterone. Further studies, including clinical trials, are required to confirm the clinical usefulness of guggulsterone. However, numerous studies have demonstrated that guggulsterone modulates several transcription factors, enzymes, cytokines, and anti-apoptotic proteins that are involved in inflammation and carcinogenesis. These

studies strongly suggest that guggulsterone has substantial potential as a chemopreventive and therapeutic agent against inflammation and tumors.

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