



Googling the Guggul (Commiphora and Boswellia) for Prevention of Chronic Diseases

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Extensive research during last 2 decades has revealed that most drugs discovered today, although costs billions of dollars for discovery, and yet they are highly ineffective in their clinical response. For instance, the European Medicines Agency has approved 68 anti-cancer drugs, and out of which 39 has reached the market level with no indication of increased survival nor betterment of quality of life. Even when drugs did improve survival rate compared to available treatment strategies, most of these were found to be clinically insignificant. This is a fundamental problem with modern drug discovery which is based on thinking that most chronic diseases are caused by alteration of a single gene and thus most therapies are single gene-targeted therapies. However, extensive research has revealed that most chronic diseases are caused by multiple gene products. Although most drugs designed by man are mono-targeted therapies, however, those designed by “mother nature” and have been used for thousands of years, are “multi-targeted” therapies. In this review, we examine two agents that have been around for thousands of years, namely “guggul” from *Commiphora* and *Boswellia*. Although we are all familiar with the search engine “google,” this is another type of “guggul” that has been used for centuries and being explored for its various biological activities. The current review summarizes the traditional uses, chemistry, *in vitro* and *in vivo* biological activities, molecular targets, and clinical trials performed with these agents.

Keywords: guggul, guggulsterone, boswellia, boswellic acid, cancer, commiphora, chronic diseases

INTRODUCTION

Despite the remarkable advances made in the field of therapies for chronic diseases including cancer over the last few decades, they still present a major health burden and are the prime cause of death across the world. Most of the chronic illnesses are caused by the deregulation of multiple genes; however majority of the drugs approved by Food and Drug Administration (FDA) target single gene product or pathway only. This displays one of the major drawbacks of these synthetic drugs. In addition, these drugs are associated with different adverse side effects and hence not tolerable by patients (Siddiqui et al., 1984; Sarup et al., 2015; Kunnumakkara et al., 2017; Banik et al., 2018). Therefore, there is an urgent need to identify novel, safe, and multi-targeted agents for the prevention and treatment of these diseases (Bordoloi et al., 2016; Kunnumakkara et al., 2018).

It has been well-evidenced that natural products are effective, multi-targeted, and extremely safe as they are the roots of many traditional systems of medicine such as Ayurveda, Unani, Siddha, traditional Chinese medicine etc. (Shishodia et al., 2008; Harsha et al., 2017). One such medicine of enormous use in Ayurveda is “Guggul.” Guggul is the gum resin obtained from two different plants *Commiphora* and *Boswellia*, produced by drying the white sap of 15–20 years old tree for a year (Figure 1; Hanus et al., 2005).

The history of guggul goes as far back as 1700 BC. Ancient script on medicine and surgery; *Sushrut Samhita*, describes that guggul when taken orally can cure internal tumors, malignant sores, obesity, liver dysfunction, intestinal worms, leucoderma, sinus, and edema. It is also used as an Ayurvedic medicine for the prevention and treatment of various other diseases such as inflammatory bowel disease (IBD), ulcers, arthritis, cardiovascular diseases (CVDs), diabetes etc. (Shishodia et al., 2008). The main ingredients of guggul are guggulsterone (GS) and boswellic acid (BA) which are obtained from *Commiphora* and *Boswellia* respectively. It also contains a huge number of lignans and ketosterols, which contributes to the vivid health beneficiary effects of guggul (Arora et al., 1971, 1972; Kimura et al., 2001; Zhu et al., 2001; Francis et al., 2004).

According to Pubmed; “google,” there are 449 publications on *Commiphora*, 519 on *Boswellia*, 207 on guggulsterone, 329 on boswellic acid, and 90 on guggul with earliest being in 1960 describing the “Antiarthritic and anti-inflammatory activity of the gum “guggul”; and in 1969 on “Analgesic effect of the gum resin from *Boswellia serrata*.” Some of the major species include *Commiphora wightii* (guggul), *Commiphora mukul*, *Commiphora gileadensis*, *Boswellia serrata* (salai guggul), *Boswellia carterii*, *Boswellia sacra* (source of frankincense & gum resin), *Boswellia ovalifoliolata*, *Boswellia dalzielii*, *Boswellia frerean*, and *Boswellia*

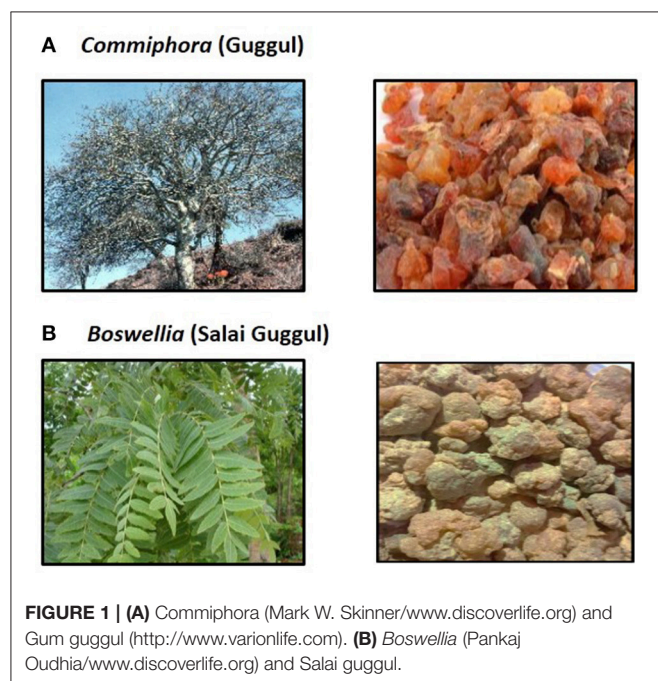
thurifera. What is common among all these plants and their products is that all of them exhibit anti-inflammatory activities, although to a variable extent. The current review describes the traditional uses, chemistry, molecular targets, *in vitro*, *in vivo* and clinical studies of guggul isolated from *Commiphora* and *Boswellia*.

SOURCE AND CHEMICAL CONSTITUENTS OF COMMIPHORA AND BOSWELLIA

The guggul tree which belongs to the family *Burseraceae*, is mainly found in the dry regions of the Indian subcontinent mainly India, Pakistan and Bangladesh. The oleogum resin of *C. mukul* (guggul tree) is a yellowish substance that is tapped during winter and ~700–900 g of resin is obtained from each tree (Deng, 2007; Shishodia et al., 2015; Yamada and Sugimoto, 2016). The guggul or balsam or the oleo gum resin is found in the balsam canals in the phloem of the large veins of leaf and base of the stem. It is a complicated mixture of minerals, gum, terpenes, sterols (Guggulsterol -I,-II,-III,-IV,-V), essential oils, sterones (Z-, E-, M-guggulsterone, and dehydroguggulsterone-M), ferrulates, lignans, and flavanones. The ethyl acetate soluble fraction also known as guggulipid, consists of various bioactive components like diterpenoids, triterpenoids, steroids, lignans, and fatty tetrol esters. Based on the pH gradient, further fractionation yields 95% neutral, 4% acidic, and 1% basic fractions. The neutral fraction when subjected to further fractionation produces 88% non-ketonic and 12% ketonic fractions. A large number of steroids including the two isomers E-(cis-) and Z-(trans-) GS [4, 17(20)-pregnadiene-3, 16-dione] were obtained from the ketonic fraction. Nearly 5% guggulipid and 2% gum guggul by weight is present in the GS (Figure 2A; Deng, 2007; Shishodia et al., 2008, 2015; Sarup et al., 2015).

Phenolics are common natural products found in plants and possess substantial antioxidant and anti-inflammatory effects. Various phenolic compounds such as hydroxybenzoic acid derivatives such as gallic acid, protocatechuic acid, gentisic acid, vanillic acid, p-hydroxy benzoic acid, syringic acid, ellagic acid, and cinnamic acid derivatives which include caffeic acid, chlorogenic acid, ferulic acid, sinapic acid (SA), and p-coumaric acid are largely present in plants. These phenolic compounds are predominantly available in guggul as well, which in part contributes to its immense biological function against diverse human chronic diseases (Hazra et al., 2018).

Guggulsterone is the only known antagonist of farnesoid X receptor (FXR). This FXR, also known as NR1H4 (nuclear receptor subfamily 1, group H, member 4), is a bile acid receptor (BAR). Bioinformatics studies (molecular docking simulation) revealed that GS binds to FXR and nuclear factor-kappa B (NF-κB) and it docks into two non-canonical binding sites of FXR, helix 1-loop-helix 2 loop and parts of helix—helix 8 including helix 8-loop-helix 9 (Meyer et al., 2005; Yang et al., 2014). Different bile acids and chenodeoxycholic acids act as natural ligand for FXR, whose expression is elevated in the liver and intestine. When FXR binds to its ligand, it gets activated



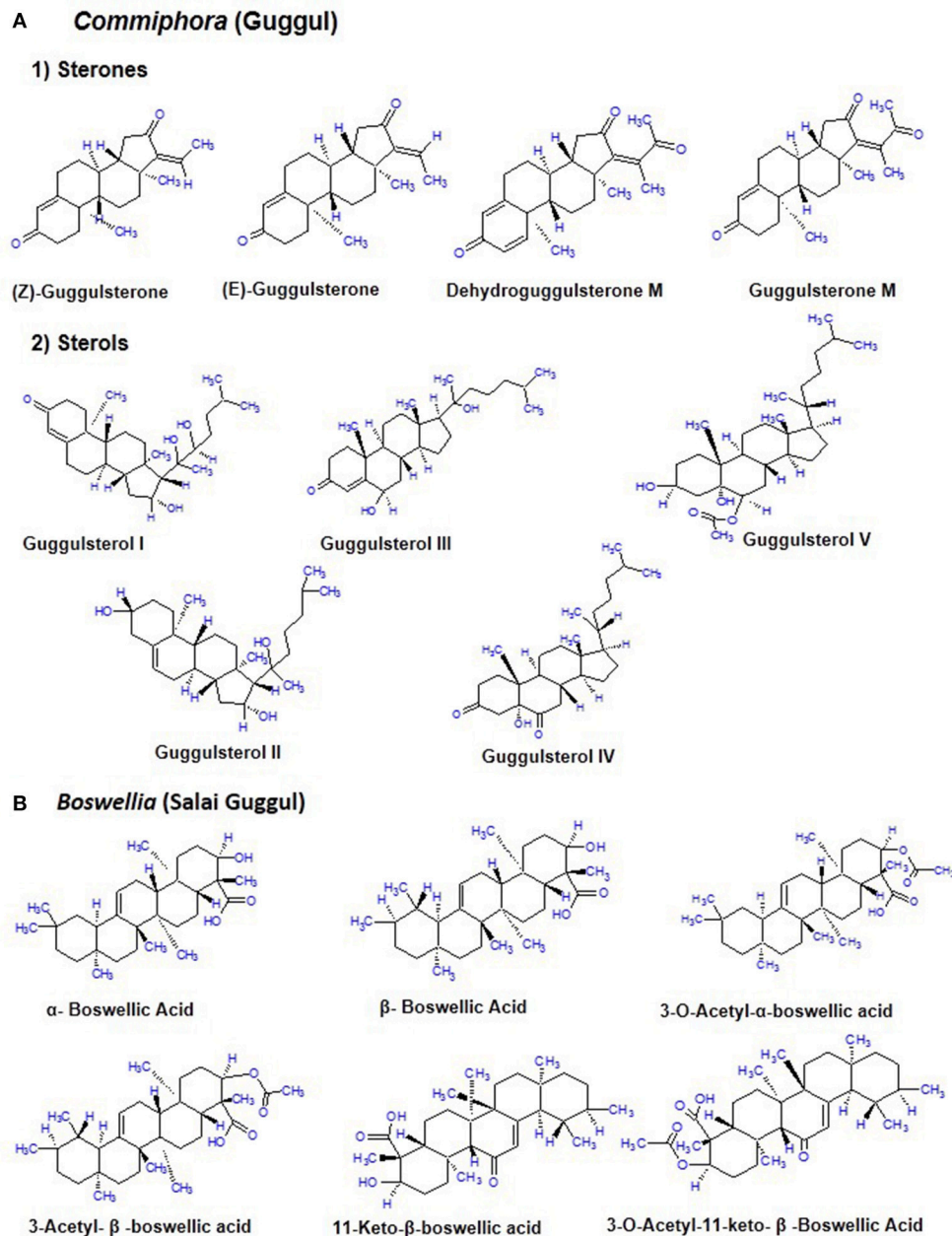


FIGURE 2 | Chemical constituents of *Commiphora* (guggul) and *Boswellia* (Salai guggul) (A) *Commiphora* (B) *Boswellia*.

and reaches the cell nucleus, where it forms a heterodimer with RXR. This heterodimer binds to the hormone response elements on DNA and regulates various genes. FXR activation downregulates cholesterol 7 α -hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis from cholesterol by inducing the expression of small heterodimer partner (SHP) which in turn inhibits the transcription of CYP7A1 gene. While obeticholic acid, fexaramine, cafestol, and chenodeoxycholic acid act as agonist of FXR; GS, from the gum resin of guggul has also been confirmed to inhibit pro-inflammatory signals, together with transcription factor NF- κ B (Sharma and Sharma, 1977; Urizar et al., 2002; Shishodia et al., 2008; Yamada and Sugimoto,

2016). Another study reported that the inhibitory activity of NF- κ B is due to the binding of GS to the RH domain of NF- κ B precursor protein p105 containing important sequences for DNA binding and dimerization (Khan et al., 2013).

B. serrata, commonly known as salai guggul, Indian olibanum, loban, or kundur, belongs to the *Burseraceae* family and is found in dry mountainous regions of India, Northern Africa, and the Middle East. *Burseraceae* family includes 17 genera and 600 species of plants. The genus *Boswellia* has 25 different species distributed throughout the tropical regions. *B. serrata* is one such medicinal plant which exhibits immense potential to combat various chronic disorders. The active pharmacological principle

of the oleo gum resin from the trees of different *Boswellia* species is the BA (Büchle et al., 2003; Du et al., 2015; Roy et al., 2016). The gum resin of the *Boswellia* species mainly consists of mucus, resin acids, and volatile oil with different quantitative composition from species to species. The gum resin of salai guggul contains pentacyclic triterpenic acids, namely α -boswellic acids, β -boswellic acids, γ -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid (KBA), acetyl-11-keto- β -boswellic acid (AKBA), and tetracyclic triterpenic acids like tirucallic acids viz 3-oxotirucallic acid, 3-hydroxytirucallic acid, and 3-acetoxytirucallic acid (**Figure 2B**). Other oleo gum resin compounds which display biological activities are: betulinic acid, lupenoic acid, epi-lupeol, isoincenseol, isoincenseol acetate and 1-ursene-2-diketone-incenseol acetate along with few other terpenes that can be found in volatile oil (Du et al., 2015; Ammon, 2016; Roy et al., 2016).

MOLECULAR TARGETS OF COMMIPHORA AND BOSWELLIA

GS suppresses the physiological action of the FXR which is a nuclear hormone receptor that controls the synthesis and transport of bile acid (Sinal and Gonzalez, 2002; Urizar et al., 2002). However, it increases the transcription of bile salt export pump (BSEP) which is majorly involved in hepatic bile acid transport (Cui et al., 2003). Besides regulating transport of bile acid, GS is a potent anti-inflammatory agent which suppresses LPS-induced NO production (Meselhy, 2003). GS has also been reported to inhibit the activation of NF- κ B by suppressing the levels of receptor activator of NF- κ B ligand (RANKL) (Ichikawa and Aggarwal, 2006). In 2004, Shishodia and group reported that GS suppressed the activation of NF- κ B and I κ B- α kinase and exhibited antiproliferative activity by inhibiting c-Myc and cyclin D1. Furthermore, GS has also been found to exert anti-metastatic effect through reducing the levels of MMP-9, COX-2, and VEGF (Shishodia and Aggarwal, 2004). This group also reported that GS induced apoptosis by modulating the expression of anti-apoptotic genes, IAP1, XIAP, Bcl-2, cFLIP, Bfl-1/A1, and survivin (Shishodia and Aggarwal, 2004). Further, GS has also been found to induce tumor cell apoptosis by activating the apoptotic genes, caspase-3, -8, -9, and inducing the release of cytochrome c, cleavage of bid and PARP. This was controlled by activated mitogen-activated protein kinase 4 (MKK4) mediated upregulation of c-Jun N-terminal kinase (JNK) and suppression of Akt. The antiproliferative activity of GS was found to be supported by reduced levels of cyclin D1, cdc2, and simultaneous upregulation of cyclin-dependent kinase inhibitors p21 and p27 (**Figure 3A**; Shishodia et al., 2007).

Boswellic acid is known to inhibit leukotriene synthesis by inhibiting 5-lipoxygenase (5-LOX) (Safayhi et al., 1992, 1995; Ammon et al., 1993). This 5-LOX inhibitor has also been found to reduce the activity of human leukocyte elastase (HLE) *in vitro* (Safayhi et al., 1997). Suppression of these molecules contributes to anti-inflammatory action of *Boswellia*. *Boswellia* is also known to induce apoptosis in cancer cells. In 2007, Bhushan and group reported that a triterpenediol from *B. serrata* induced apoptosis

in HL-60 cells through both intrinsic and extrinsic pathways (Bhushan et al., 2007). In the first case, the triterpenediol was found to disturb the mitochondrial membrane potential, reduce Bcl-2/Bax ratio and cause release of AIF, Smac/DIABLO, and cytochrome c from the mitochondria along with suppression of survivin and upregulation of caspases-3, -8, and -9, thereby leading to the cleavage of ICAD and PARP while in the second case, the oxidative stress generated in the cells due to excessive ROS and NO production triggered the activation of TNF-R1 and DR4 followed by activation of caspase-8. Another study in multiple myeloma cells also suggested that BA acetate induces apoptosis by upregulating death receptor proteins, DR4 and DR5 which subsequently leads to the activation of caspase-8 followed by caspase-3 (Xia et al., 2005). The role of DR5-mediated pathway which involves activation of CAAT/enhancer binding protein homologous protein (CHOP) was reported in AKBA-mediated apoptosis of prostate cancer cells (Lu et al., 2008). Caspase-8 activation has also been reported in other BA-induced apoptosis studies (Liu et al., 2002a,b). In 2002, Park et al. hypothesized that AKBA contributed in the process of proliferation and apoptosis of tumors by inhibiting platelet-derived growth factor (PDGF)-stimulated extracellular signal-regulated kinase 1 and 2 (ERK-1 and ERK-2) (Park et al., 2002b). BA mediated apoptosis has also been evident in cancer cells via activation of p21, an important cell cycle regulator protein (Glaser et al., 1999; Liu et al., 2006). Apart from this, AKBA has been found to interfere with IL-6-induced STAT3 signaling via protein tyrosine phosphatase SHP-1 subsequently causing downregulation of cyclin D1, Bcl-2, Bcl-xL, Mcl-1, and VEGF, thus impeding proliferation, survival and angiogenesis of multiple myeloma cells (Kunnumakkara et al., 2009). Moreover, BA has also been found to suppress metastatic growth factor, basic fibroblast growth factor (bFGF), chemokine receptor; CXCR4 and angiogenic factor; VEGFR 2 (Singh et al., 2007; Pang et al., 2009; Park et al., 2011a). Further, *in vivo* studies have unveiled that BA regulates proliferation and metastasis of cancer cells by downregulating other targets like COX-2, c-Myc, cyclin D1, MMP-9, VEGF, ICAM-1, Bcl-2, Bcl-xL, survivin, and cellular inhibitor of apoptosis protein 1 (IAP-1) (Park et al., 2011a,b; Yadav et al., 2012). Most of these genes are regulated by the transcription factor, NF- κ B which is also downregulated by BA (Syrovets et al., 2005a,b; Takada et al., 2006). Furthermore, BA has also been shown to regulate the activity of P-glycoprotein (Pgp) which is an important class of drug transporters (Weber et al., 2006). It is also an inhibitor of topoisomerases I and II in cancer cells (Hoernlein et al., 1999; Syrovets et al., 2000; Zhao et al., 2003). The anticancer activity of this potential compound also involves regulation of let-7 and miR-200 microRNA family (**Figure 3B**; Takahashi et al., 2012).

THERAPEUTIC PROPERTIES OF GUGGUL

Congregate evidences show guggul to be profoundly effective against diverse chronic diseases such as Alzheimer's disease, arthritis, cancer, pancreatitis, IBD, dermatitis, diabetes, infectious diseases, intestinal metaplasia, otitis media, respiratory diseases, asthma, psoriasis, gingivitis etc. Besides, it also

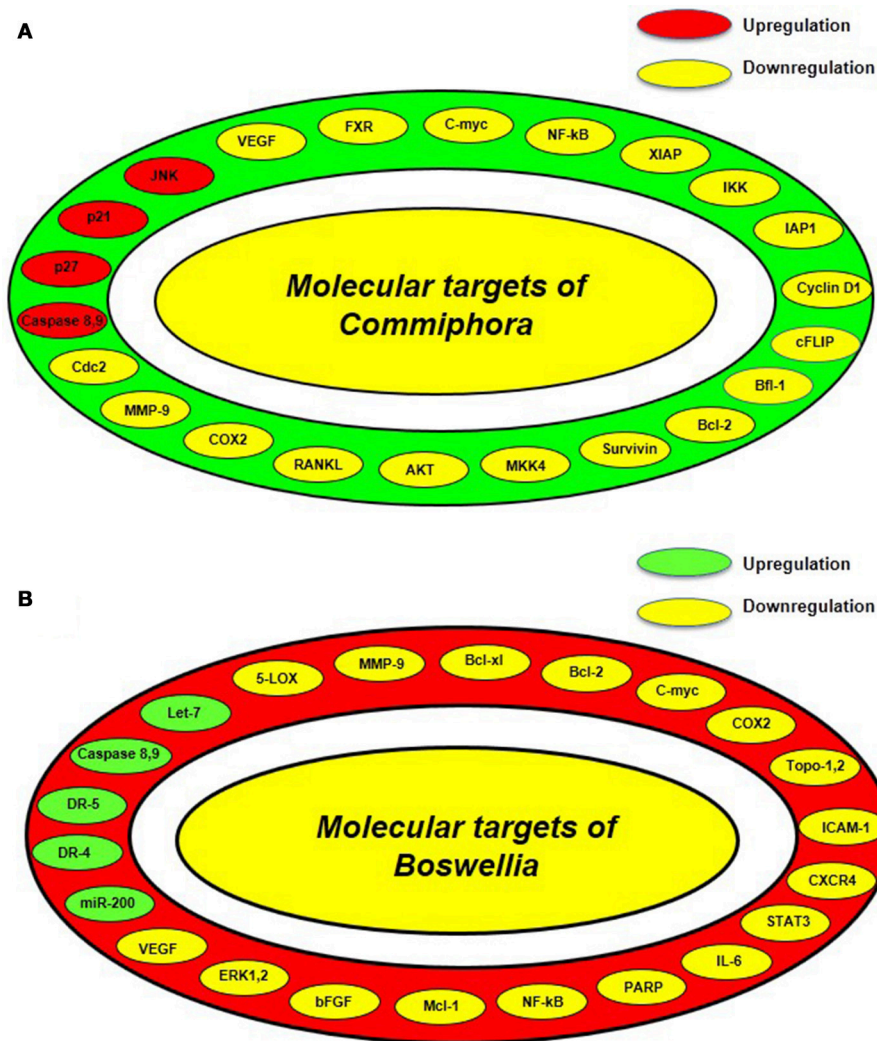


FIGURE 3 | Various molecular targets of guggul from *Commiphora* and *Boswellia* (A) Molecular targets of guggul from *Commiphora* includes Bcl2, B-cell lymphoma 2; CDC 2, cell division cycle kinase 2; c-FLIP, cellular caspase-8 (FLICE)-like inhibitory protein; COX, cyclooxygenase; FXR, farnesoid X receptor; IKK, IκB kinase; IAP, Inhibitors of apoptosis proteins; JNK, c-Jun N-terminal kinase; MKK4, mitogen-activated protein kinase kinase 4; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; RANKL, Receptor activator of nuclear factor kappa-B ligand; VEGF, vascular endothelial growth factor; XIAP, x-linked inhibitor of apoptosis protein.

(B) Molecular targets of guggul from *Boswellia* includes Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra-large; CXCR-4, C-X-C chemokine receptor type 4; DR, Death receptor; 5-LOX, 5-Lipoxygenase; MMP, Matrix metalloproteinase; NF-κB, nuclear factor-κB; Topo, Topoisomerase; ICAM-1, Intercellular adhesion molecule 1; STAT-3, Signal transducer and activator of transcription 3; IL-6, Interleukin 6; PARP, Poly ADP ribose polymerase; Mcl-1, Myeloid leukemia cell differentiation protein; bFGF, Basic fibroblast growth factor; ERK-1,-2, Extracellular signal-regulated kinases.

exerts hepatoprotective, neuroprotective, anti-inflammatory, anti-oxidant, cardioprotective, hypolipidemia, and thyroid stimulatory effect by targeting multiple signaling pathways (Table 1; Figure 4).

IN VITRO STUDIES WITH COMMIPHORA AND BOSWELLIA AND THEIR ROLE IN DIFFERENT CHRONIC DISEASES

Numerous *in vitro* studies have indicated the efficiency of guggul against diverse chronic diseases including cancer (Shishodia et al., 2007, 2008; Singh S. V. et al., 2007; Shah et al., 2012; Roy et al.,

2016). GS induced apoptosis in cancer cells via inhibition of NF-κB, activation of JNK and downregulation of Akt and anti-apoptotic proteins (Shishodia and Aggarwal, 2004; Shishodia et al., 2007). Treatment with GS led to the inhibition of DNA synthesis and proliferation of leukemia cells via downregulation of cyclin D1, cdc2, and upregulation of p21 and p27 (Samudio et al., 2005; Shishodia et al., 2007). In addition, *B. serrata* gum resin displayed cytostatic and apoptosis-inducing effect against leukemia and brain tumor cells (Hostanska et al., 2002). Further, GS induced cell death in prostate cancer cells by reactive oxygen intermediate (ROI)-dependent activation of JNK, p38 MAPK and also activation of ERK1/2 (Singh S. V. et al., 2007; Xiao and Singh, 2008). Additionally, AKBA inhibited the proliferation and

TABLE 1 | *In vitro* biological activities of guggul (*Commiphora* and *Boswellia*) against various chronic diseases.

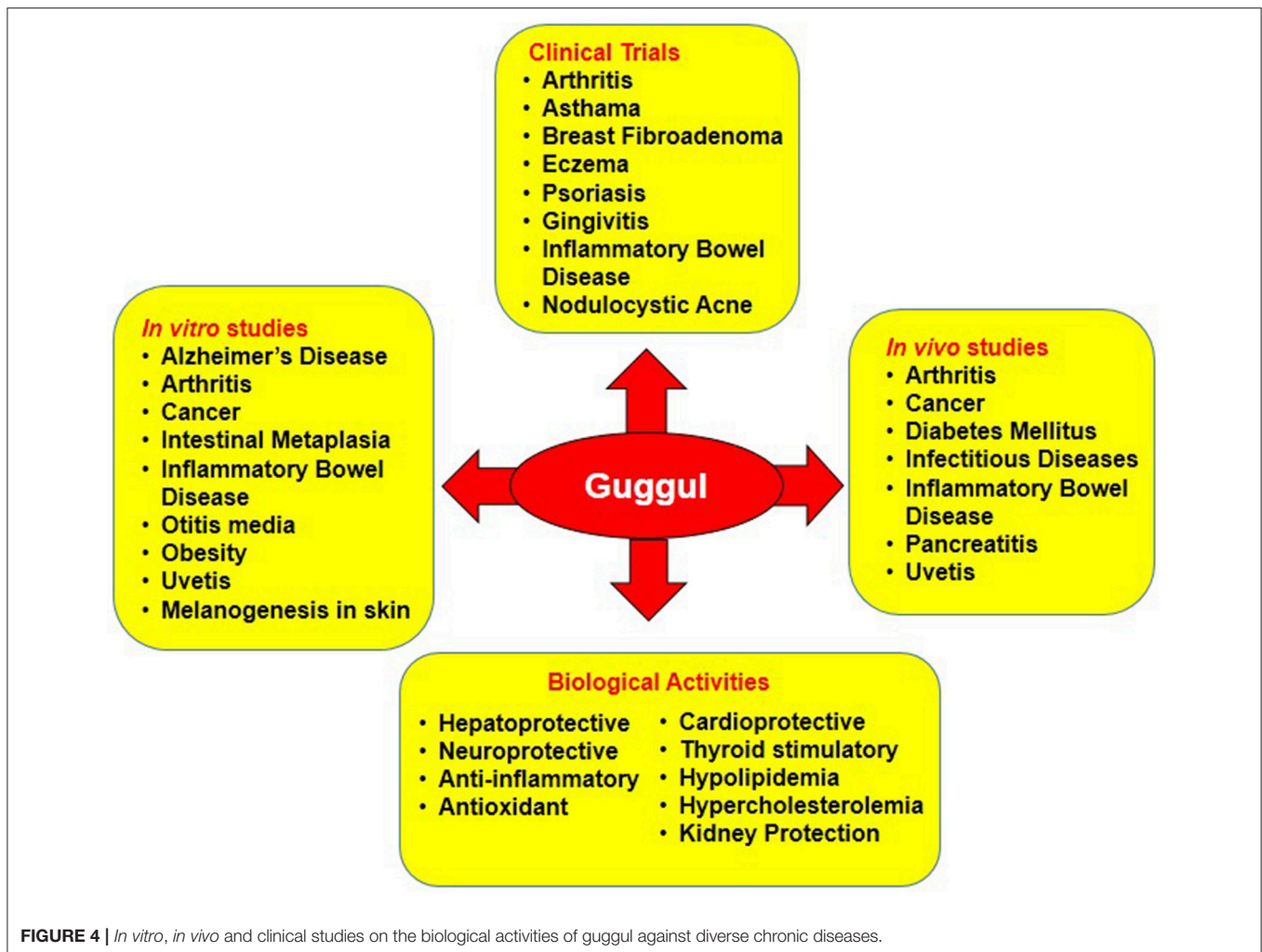
Disease	Mechanism of action	References
Arthritis	↓RANKL-induced NF-κB activation ↓IRF3 ↓NF-κB	Ichikawa and Aggarwal, 2006 ^c Youn et al., 2009 ^c Zhang et al., 2016 ^c
Barrett's esophagus	↓FXR	De Gottardi et al., 2006 ^c
CANCER		
Bladder cancer	↑EGR1, ↑ATF3, ↑DDIT3	Frank et al., 2009 ^d
Brain cancer	↑p21 ↓Erk-1, ↓Erk-2 –	Glaser et al., 1999 ^d Park et al., 2002a,b ^d Hostanska et al., 2002 ^d
Breast cancer	↓MDR ↓MDR ↓NF-κB; ↓IGF1-Rβ; ↓ERα ↓Wnt/β-Catenin; ↓cyclin D1; ↓C-myc ↑Ho-1; ↑Nrf-2; ↑ROS & ↑p-Akt ↑BCRP; ↓MDR	Xu et al., 2011 ^c Xu et al., 2012 ^c Choudhuri et al., 2011 ^c Jiang et al., 2013 ^c Almazari et al., 2012 ^c Kong et al., 2015 ^c
Cervical cancer	↑P-gp & MRP1 ↓PARP; ↓NF-κB	Nabekura et al., 2008 ^c Qurishi et al., 2012 ^d
Cholangiocarcinoma	↓Survivin; ↓Bcl-2 ↓ROS/JNK	Zhong et al., 2015 ^c Zhong et al., 2016 ^c
Colorectal cancer	↓STAT3 & VEGF ↓NF-κB; ↓IGF1-Rβ; ↓ERα ↑Caspase-8 ↑p21; ↓cyclin D1,-E; ↓CDK-2,-4 ↓PARP ↑let-7 and miR-200 families ↑SAMMD14; ↑SMPD3, ↓DNMT activity	Kim et al., 2008 ^c Choudhuri et al., 2011 ^c Liu et al., 2002b ^d Liu et al., 2006 ^d Qurishi et al., 2012 ^d Takahashi et al., 2012 ^d Shen et al., 2012 ^d
Esophageal cancer	↓CdX2 ↓NF-κB; ↓COX-2	Yamada et al., 2014 ^c Yamada et al., 2014 ^c
Gall bladder cancer	↓NF-κB	Yang et al., 2012 ^c
Glioma	↓Ras; ↓NFκB ↓Topoisomerase I	Dixit et al., 2013 ^c Hoernlein et al., 1999 ^d
Head and Neck	↑JNK; ↓Akt ↓STAT3 ↓Bcl-2; ↓XIAP; ↓cyclin D1; ↓c-myc ↓PI3K/Akt, ↓NF-κB; ↓STAT3 ↓p-STAT3; ↓STAT3	Shishodia et al., 2007 ^c Li et al., 2009 ^c Macha et al., 2010 ^c Macha et al., 2011b ^c Macha et al., 2011a ^c
Leukemia	↑JNK; ↓Akt ↓NF-κB ↓IKK ↓BAR ↑Externalization of PS ↓P-gp – – ↑Caspase-8, ↑DR4, ↑DR5 ↓NF-κB ↓Topoisomerase I, ↓Topoisomerase II ↓PI3K/Akt/Hsp-90 cascade – – ↓P-gp; ↓COX-2; ↓Prostaglandin E2	Leeman-Neill et al., 2009 ^c Shishodia et al., 2007 ^c Shishodia and Aggarwal, 2004 ^c Wu et al., 2002 ^c Samudio et al., 2005 ^c Xu et al., 2012 ^c Jing et al., 1999 ^d Hostanska et al., 2002 ^d Xia et al., 2005 ^d Takada et al., 2006 ^d Chashoo et al., 2011 ^d Khan et al., 2012 ^d Shao et al., 1998 Huang et al., 2000 ^c Xu et al., 2014a

(Continued)

TABLE 1 | Continued

Disease	Mechanism of action	References
Liver cancer	↓Cox-2; ↓P-gp ↑CHOP-dependent DR5 ↓TGF-β1; ↓VEGF ↓BAR ↓CYP7A1 ↑Caspase-8	Xu et al., 2017 ^c Moon et al., 2011 ^c Shi et al., 2015 ^c Wu et al., 2002 ^c Owsley and Chiang, 2003 ^c Liu et al., 2002a ^d
Lung cancer	↑JNK; ↓Akt ↓PARP	Shishodia et al., 2007 ^c Qurishi et al., 2012 ^d
Melanoma	↓Tyrosinase ↑JNK; ↓Akt ↓Topoisomerase II, ↓MMPs	Koo et al., 2012 ^c Shishodia et al., 2007 ^c Zhao et al., 2003 ^d
Meningioma	↓Erk-1, ↓Erk-2	Park et al., 2002a ^d
Myeloma	↓STAT3 ↓p-STAT3; ↓pJAK2; ↓p-c-Src; ↓SHP-1; ↓STAT3; ↓Bcl-2; ↓Mcl-1; ↓cyclin D1; ↓VEGF; ↑Caspase-3 and ↓PARP	Kunnumakkara et al., 2009 ^d Ahn and Youn, 2008 ^c
Pancreatic cancer	↓NF-κB; ↓IGF1-Rβ; ↓ERα ↓NF-κB	Choudhuri et al., 2011 ^c Park et al., 2011b ^d
Prostate cancer	↑JNK ↓JAK/STAT ↑Bax; ↑Bak ↑PSA ↑JNK ↓NF-κB ↑Caspase 3 ↑DR5, ↑CHOP, ↑caspase-8, ↓PARP ↓AR, ↑p21, ↓cyclin D1 ↓mTOR ↓MMP, ↓PARP-1 ↓VEGF, ↓FGF, ↓G-CSF, ↓MMP-2, ↓IL-17, ↓VEGF-R2	Xiao et al., 2011 ^c Macha et al., 2013 ^c Singh et al., 2005 ^c Burris et al., 2005 ^c Singh et al., 2007b ^c Syrovets et al., 2005b ^d Büchle et al., 2006 ^d Lu et al., 2008 ^d Yuan et al., 2008 ^d Morad et al., 2013 ^d Pathania et al., 2015 ^d Xiao and Singh, 2008 ^c
Neuroblastoma	↓PARP	Qurishi et al., 2012 ^d
Cardiotoxicity	↓Caspase-3	Wang et al., 2012 ^c
Chikungunya	↓Entry of CHIKV Env pseudotyped lentiviral vectors	von Rhein et al., 2016 ^d
Gastric intestinal metaplasia	↓CdX2	Xu et al., 2010 ^c
Hepatic fibrosis	↓NF-κB	Kim et al., 2013 ^c
Kidney injury in systemic infection	↓NF-κB	Kim et al., 2016 ^c
Nephrotoxicity	↓MAPK	Lee et al., 2017 ^c
Neuroinflammation	↓IκBα - ↓NF-κB	Huang et al., 2016 ^c
Obesity	↑Caspase-3; ↓PPARγ2, ↓C/EBP-α,-β	Yang et al., 2008 ^c
Otitis media	↓NF-κB	Song et al., 2010 ^c

AR, Androgen receptor; ATF3, Activating transcription factor 3; BAR, Bile acid receptor; BCRP, Breast cancer resistance protein; c, *Commiphora*; C/EBP, CCAAT/enhancer binding protein; CDK, Cyclin dependent kinase; CdX2, Caudal-related homeobox 2; CHOP, CAAT/enhancer binding protein homologous protein; COX-2, Cyclooxygenase-2; CYP7A1, Cholesterol 7α-hydroxylase; d, *Boswellia*; DDIT3, DNA damage inducible transcript 3; DNMT, DNA methyl-transferase; DR, Death receptor; EGR1, Early growth response 1; ERα, Estrogen receptor alpha; FXR, Farnesoid X receptor; G-CSF, Granulocyte colony-stimulating factor; HO-1, Heme oxygenase-1; Hsp90, Heat shock protein 90; IGF1, Insulin-like growth factor 1; JNK, c-Jun N-terminal kinase; IL, Interleukin; IRF3, Interferon-regulatory factor 3; MAPK, Mitogen-activated protein kinase; MCL-1, myeloid leukemia cell differentiation protein; MDR, Multidrug resistance; MMP, Matrix metalloproteinases; MRP, Multidrug resistance protein; mTOR, Mechanistic target of rapamycin; NF-κB, Nuclear factor kappa B; Nrf-2, The nuclear factor erythroid 2 (NFE2)-related factor 2; PARP, Poly ADP ribose polymerase; PI3K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; PPAR, Peroxisome proliferator activated receptor; pRb, phosphorylated Retinoblastoma; PS, Phosphatidylserine; PSA, Prostate-specific antigen; RANKL, Receptor activator of nuclear factor kappa-B ligand; ROS, Reactive oxygen species; SAMD14, Sterile Alpha Motif Domain Containing 14; SHP-1, Src homology region 2 domain-containing phosphatase-1; SMPD3, Sphingomyelin phosphodiesterase 3; STAT, Signal transducer and activator of transcription 6; STAT3, Signal transducer and activator of transcription 3; TGF, Transforming growth factor; TLR-3, Toll-like receptor-3; TLR-4, Toll-like receptor-4; VEGF, Vascular endothelial growth factor; VEGFR2, Vascular endothelial growth factor receptor 2; XIAP, X-linked inhibitor of apoptosis protein.



induced apoptosis in colon cancer cells through p21 and caspase-8 dependent pathway (Liu et al., 2002b, 2006). Besides, it also modulated the expression of let-7, miR-200 families and their downstream targets in colon cancer cells (Takahashi et al., 2012).

Apart from cancer, the effect of guggul has been well proven against different inflammatory diseases such as rheumatoid arthritis, IBD, and various other diseases such as obesity, otitis media, uveitis etc. For example, treatment with GS downregulated RANKL induced osteoclastogenesis and blocked IL-1 β mediated production of chemokines and epithelial neutrophil activating peptide-78 (ENA-78), MMP-1,-3 via suppression of NF- κ B, nuclear p50, and p65 subunit and I κ B α degradation in rheumatoid arthritis (Ichikawa and Aggarwal, 2006; Kinne et al., 2007; Lee et al., 2008; Ammon, 2016). A study conducted by Cheon and group on IBD showed that GS inhibited IL-1 β - or lipopolysaccharide (LPS)- induced ICAM-1 expression, NF- κ B transcription activity and I κ B phosphorylation/degradation in human Caco-2 cells and rat non-transformed IEC-18 cells (Cheon et al., 2006). Further, treatment with GS alone showed increase in apoptosis and lipolysis and its combination with genistein resulted in increased cleavage of procaspase-3, PARP, expression of Bax, release of cyt-c and

prevented lipid accumulation in maturing adipocytes resulting in inhibition of adipogenesis (Yang et al., 2007, 2008). GS exerted its effect against otitis media, the foremost cause of hearing impairment in children by inhibiting LPS-induced upregulation of TNF- α expression, COX-2 production and I κ B α degradation (Ovesen and Ledet, 1992; Barrett et al., 2003; Song et al., 2010). In case of uveitis, treatment with GS inhibited LPS-induced expression of inflammatory proteins in human primary non-pigment ciliary epithelial cells (Kalariya et al., 2010).

As guggul is an FXR antagonist, it is used extensively as a cholesterol-lowering agent (Rizzo et al., 2006; Shah et al., 2012). GS eliminated the effect of chenodeoxycholic acid (CDCA), an FXR agonist on the expression of Cdx2 and MUC2 and thus prevented bile acid induced gastric intestinal metaplasia and carcinogenesis (Xu et al., 2010). Oswley and Chiang reported that GS antagonizes FXR induction of BSEP but activates pregnane X receptor to inhibit CYP7A1 gene (Oswley and Chiang, 2003). In addition, *Commiphora* and *Boswellia* showed potent cardioprotective as well as thyroid-stimulatory effects (Singh et al., 1982; Deng, 2007). For instance, GS inhibited DOX induced cytotoxicity, reduced apoptosis, and intracellular ROS and formation of MDA in DOX-treated H9C2 cells (Wang

et al., 2012). In addition, triterpenes and prenylaromadendrane-type diterpenes from the gum resin of *B. carterii* was shown to exert hepatoprotective effect against d-galactosamine-induced liver cell damage (Wang et al., 2013, 2016).

IN VIVO STUDIES WITH COMMIPHORA AND BOSWELLIA AND THEIR ROLE IN DIFFERENT CHRONIC DISEASES

Promising after effects of *Commiphora* and *Boswellia* against various chronic diseases in the *in vitro* setting has led to a handful of *in vivo* studies where the efficacy of guggul was evaluated in different experimental models of diverse chronic diseases such as cancer, inflammatory, cardiovascular, and metabolic diseases, atherosclerosis, asthma etc. (Table 2; Figure 4). Recently, several studies have reported the anti-tumor efficacy of guggul in different cancers such as cancers of breast, esophagus, head, and neck, pancreas, prostate etc. (An et al., 2009). For instance, AKBA was found to prevent intestinal tumorigenesis and exert chemopreventive effect via inhibition of wnt/ β -catenin and NF- κ B/COX-2 signaling pathways (Liu et al., 2013; Wang R. et al., 2014). Another study showed AKBA to function via modulation of let-7 and miR-200 downstream genes in colorectal (CRC) tumors (Takahashi et al., 2012). In case of breast cancer, treatment with GS increased the chemosensitivity of MCF-7/DOX cells to doxorubicin *in vivo* through inhibition of Bcl-2 and Pgp (Xu et al., 2014b). In addition, GS suppressed esophageal tumor cell viability via inhibition of FXR and prevented the growth of esophageal cancer cells significantly in combination with amiloride *in vivo* (Guan et al., 2013, 2014). Furthermore, in case of glioma, cyano enone of methyl boswellates (CEMB), and 3- α -propionyloxy- β -boswellic acid (POBA) significantly inhibited the tumor growth in murine models (Ravanan et al., 2011; Qurishi et al., 2013). Again, topical application of Boswellin (BE); *B. serrata* gum resin exudate inhibited skin inflammation, epidermal proliferation, and tumor promotion induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mice. Additionally, treatment with guggulipid was shown to cause reduced growth of HNSCC cells *in vivo* (Leeman-Neill et al., 2009). Besides, GS enhanced the antitumor efficacy of gemcitabine in pancreatic cancer via modulation of Akt, NF- κ B, and apoptosis-related proteins (Ahn et al., 2012). In case of prostate cancer as well, guggul has been found to be highly effective *in vivo* (Syrovets et al., 2005b; Büchele et al., 2006; Pang et al., 2009; Pathania et al., 2015). Oral administration of guggulsterone prevented *in vivo* angiogenesis of prostate cancer cells through suppression of VEGF-VEGF-R2-Akt signaling (Xiao and Singh, 2008).

Apart from cancer, the efficacy of guggul was well proven in different inflammatory diseases such as arthritis, colitis, gastritis, IBD, pancreatitis, uveitis etc. (Sharma et al., 1989; Cheon et al., 2006; Xiao and Singh, 2008; Mencarelli et al., 2009; Kalariya et al., 2010; Kim et al., 2010, 2013; Dhaneshwar et al., 2013; Kang et al., 2013; Wang R. et al., 2014). In case of rheumatoid arthritis, treatment with guggul decreased the thickness of joint swelling, reduced the infiltration of leucocytes into the pleural cavity,

suppressed the pro-inflammatory cytokines and increased beta-glucuronidase activity *in vivo* (Sharma and Sharma, 1977; Reddy and Dhar, 1987; Sharma et al., 1989; Fan et al., 2005). In addition, guggul reduced the severity of IBD via inhibition of LPS- or IL-1 β -induced ICAM-1 gene expression and NF- κ B activity (Kriegelstein et al., 2001; Cheon et al., 2006; Mencarelli et al., 2009; Kim et al., 2010). Furthermore, administration of GS resulted in mitigation of histological damage, suppressed serum lipase levels, inhibition of infiltrations of neutrophils, and macrophages and decreased cytokine production in pancreatitis (Kim et al., 2015). Moreover, GS inhibited the expression of endotoxin-induced uveitis (EIU)-associated inflammatory markers such as MMP-2, NO, and prostaglandin E₂ (PGE₂) (Kalariya et al., 2010).

Guggul exhibited profound cardioprotective effects as well *in vivo* (Chander et al., 2003). It decreased the lipid peroxide, creatine phosphokinase, phospholipase, xanthine oxidase activities, and total cholesterol level in the serum; increased superoxide dismutase (SOD), myocardial antioxidants, glutathione peroxidase (GSHPx), catalase (CAT); reduced glutathione (GSH), creatine-phosphokinase-MB (CK-MB), and lactate dehydrogenase (LDH) as well as reversed the cardiac damage induced by isoproterenol (Kaul and Kapoor, 1989; Batra et al., 2000; Ojha et al., 2011). The hypolipidemic effect of guggul has also been well studied in different animal models (Khanna et al., 1969; Dixit et al., 1980; Baldwa et al., 1981; Lata et al., 1991). Guggul diminished hyperlipidemia via inhibition of FXR activation. In high-fat-diet-fed mice, treatment with GS improved blood glucose in fasting condition, plasma insulin level, glucose tolerance, level of harmful lipids, phosphoenol pyruvate carboxykinase, glucose-6-phosphatase, and other proteins like glucose transporter-4, PPARc, and TNF- α (Satyavati et al., 1969; Singh et al., 1990; Urizar et al., 2002; Cui et al., 2003; Sharma et al., 2009; Tripathi, 2009). Further, *C. opobalsamum*, *C. mukul*, *B. serrata*, and *B. ovalifoliolata* species mitigated hepatic damage and displayed protective effect against lipid peroxidation and deviated serum enzymatic variables (Al-Howiriny et al., 2004; Y et al., 2006; Mahesh et al., 2014). In addition, GS reversed neuronal damage and memory deficits in mice by increasing glutathione level in the brains, antiacetylcholine esterase, and antioxidant activities (Saxena et al., 2007). Apart from these, administration of GS was found to increase thyroid function by enhancing iodine uptake, improved the activities of thyroid peroxidase, and protease and ameliorated hypothyroidism through its ability to increase thyroid hormone *in vivo* (Tripathi et al., 1975, 1984; Panda and Kar, 2005).

Taken together, these pre-clinical studies provide substantial evidence of the enormous potential of guggul as a multi-targeted agent for the prevention and treatment of different chronic diseases.

CLINICAL STUDIES WITH COMMIPHORA AND BOSWELLIA AND THEIR ROLE IN DIFFERENT CHRONIC DISEASES

Several clinical trials have been conducted to evaluate the effect of “guggul” from *Commiphora* and *Boswellia* on various chronic disorders. Human studies on guggul has

TABLE 2 | *In vivo* biological activities of guggul (*Commiphora* and *Boswellia*) against various chronic diseases.

Disease	Mechanism of action	References
Arthritis	↓Leucocytes –	Sharma et al., 1989 ^d Dhaneshwar et al., 2013 ^d
Asthma	↓IL-1β; ↓TLR4 ↓pSTAT6; ↓GATA3 ↓pSTAT6; ↓GATA3	Wang Q. et al., 2014 ^d Liu et al., 2015 ^d Zhou et al., 2015 ^b
Atherosclerosis	↓NF-κB	Cuaz-Pérolin et al., 2008 ^d
CANCER		
Breast Cancer	↓PCNA; ↓Ki67	Xu et al., 2014b ^c
Colon Cancer	↑Caspase-3, -8; ↓cIAP-1, -2; ↓Bcl-2 ↓Wnt/β-catenin; ↓NF-κB/COX-2 ↓Wnt/β-catenin; ↓NF-κB/COX-2 ↑let-7 and miR-200 families	An et al., 2009 ^c Liu et al., 2013 ^d Wang R. et al., 2014 ^d Takahashi et al., 2012 ^d
Ehrlich tumor	↓VEGF; ↑caspase-3; ↑Bax ↓NF-κB; ↓PARP	Agrawal et al., 2011 ^d Qurishi et al., 2012 ^d
Esophageal Cancer	↓NHE-1 ↓FXR	Guan et al., 2014 ^c Guan et al., 2013 ^c
Glioma	↓NO; ↑Caspase-3, -8 ↓AOM-induced ACF ↓NF-κB; ↓PARP	Ravanan et al., 2011 ^d Huang et al., 2000 ^d Qurishi et al., 2013 ^d
Head and Neck Pancreatic cancer	↓STAT-3; ↓HIF-1α ↓NF-κB; ↓Akt ↓NF-κB	Leeman-Neill et al., 2009 ^c Ahn et al., 2012 ^c Park et al., 2011a ^d
Prostate cancer	↓VEGF-VEGF-R2-Akt signaling ↓NF-κB ↑Caspase-3 ↓VEGFR-2 ↓MMP; ↓PARP-1	Xiao and Singh, 2008 ^c Syrovets et al., 2005b ^d Büchele et al., 2006 ^d Pang et al., 2009 ^d Pathania et al., 2015 ^d
Colitis	↓NF-κB ↓ICAM-1; ↓NF-κB	Kim et al., 2010 ^c Cheon et al., 2006 ^c
Dementia	↓AChE activity; ↓MDA; ↑GSH	Saxena et al., 2007 ^c
Depression	↑BDNF signaling; ↑Hippocampal neurogenesis	Liu et al., 2017 ^c
Diabetes	↓PPARγ	Sharma et al., 2009 ^c
Gastritis	↓NF-κB	Kim et al., 2013 ^c
Gastric injury	↑Nrf2; ↑HO-1	Zhang et al., 2016 ^d
Gastric ulcer	↑Prostaglandin; ↓leukotrienes	Singh et al., 2008 ^d
Hepatic injury	↓NF-κB; ↓p65; ↓p-JNK; ↓TLR-3, -4; ↓MyD88	Chen et al., 2016 ^d
Hyperlipidemia	↓Oxidative modification of LDL –	Wang et al., 2004 ^c Satyavati et al., 1969 ^c
Inflammatory bowel diseases	↑Plasma insulin level; ↓LDL; ↓VLDL ↓NF-κB ↓IL-2, -4; ↓IFN-γ	Sharma et al., 2009 ^c Kang et al., 2013 ^c Mencarelli et al., 2009 ^c
Ischemia reperfusion	↑Nrf2; ↑HO-1 ↑Nrf2; ↑HO-1	Ding et al., 2014 ^d Ding et al., 2015 ^d
Memory impairment	↑CREB-BDNF signaling	Chen et al., 2016 ^c
Myocardial ischemia	↓Oxidative degradation of lipids; ↓ROS ↓Lipid peroxides; ↓XO; ↑SOD	Chander et al., 2003 ^c Kaul and Kapoor, 1989 ^c
Pancreatitis	↓NF-κB; ↓IL-6; ↓Chemokine-1, -10	Kim et al., 2017 ^c
Thyroid dysfunction	↑Iodine uptake ↑Iodine uptake	Tripathi et al., 1975 ^c , 1984 ^c Panda and Kar, 2005
Uveitis	↓NF-κB; ↓MMP-2; ↓iNOS; ↓COX-2	Kalariya et al., 2010 ^c

ACF, Aberrant crypt foci; AChE, Acetylcholinesterase; AOM, azoxymethane; BCRP, Breast cancer resistance protein; BDNF, Brain-derived neurotrophic factor; c, *Commiphora*; cIAP, The cellular inhibitor of apoptosis; COX-2, Cyclooxygenase-2; CREB-BDNF, cAMP-response element binding protein-BDNF d, *Boswellia*; FXR, Farnesoid X receptor; GSH, Glutathione; HIF-1α, Hypoxia-inducible factor 1-alpha; HO-1, Heme oxygenase-1; ICAM, Intracellular adhesion molecules; IFN, Interferon; IκB, Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor IL, Interleukin; IL-1β, Interleukin 1 beta; iNOS, Inducible nitric oxide synthase; LDL, Low density lipoprotein; MDA, Malondialdehyde; MDR, Multidrug resistance; MMP, Matrix metalloproteinases; MyD88, Myeloid differentiation primary response 88; NF-κB, Nuclear factor kappa B; NHE-1, Na⁺/H⁺-exchanger-1; NO, Nitric oxide; Nrf-2, The nuclear factor erythroid 2 (NFE2)-related factor 2; p-JNK, Phosphorylated Jun N-terminal kinases; P-gp, P-glycoprotein; PARP, Poly ADP ribose polymerase; PCNA, Proliferating cell nuclear antigen; PPAR, Peroxisome proliferator activated receptor; pSTAT6, phosphorylated Signal transducer and activator of transcription 6; ROS, Reactive oxygen species; SOD, Superoxide Dismutase; STAT, Signal transducer and activator of transcription; TLR, Toll-like receptor; VEGF, Vascular endothelial growth factor; VEGFR2, Vascular endothelial growth factor receptor 2; XO, Xanthine oxidase.

been found to be effective against different diseases such as asthma, breast fibroadenoma, chronic kidney disease, colitis, Crohn's disease, fascioliasis, hepatitis C, hypercholesterolaemia, hyperlipidemia, metabolic syndrome, nodulocystic acne, arthritis, schistosomiasis, stress urinary incontinence etc. (Table 3; Figure 4).

Arthritis

Arthritis is mainly caused due to inflammation of joints, the tissues surrounding the joints and other connective tissues. Osteoarthritis is the most common form of arthritis which affects a wide range of people across all the places. As guggul has been reported to exhibit high affectivity against arthritis pre-clinically; hence, its effect was evaluated in the clinical setting as well. In one such study, 30 patients with arthritis were treated with gum guggul for 1 month which resulted in remarkable improvement in the total scores of Western Ontario and MacMaster Osteoarthritis Index and condition of the patients (Singh et al., 2003). Another study was conducted by Kimmatkar et al., to check the safety, tolerability, and efficacy of *B. serrata* extract in 30 patients with knee osteoarthritis. The patients receiving drug treatment reported a decrease in knee pain and swelling of the knee joint as well as increased knee flexion and walking distance (Kimmatkar et al., 2003).

Asthma

Asthma is a chronic multifactorial inflammatory disease of the respiratory tract and is one of the major health concern. Notably, *Boswellia* has been found to be effective in the treatment of this disease. In a clinical study, 40 patients having 23 males, and 17 females in the age range of 18–75 years, suffering from bronchial asthma were treated with 300 mg of gum resin thrice daily for a period of 6 weeks. This led to improved prognosis in around 70% of the patients as various signs and symptoms of bronchial asthma like rhonchi, dyspnoea, and attacks disappeared upon treatment (Gupta et al., 1998).

Breast Fibroadenomas

Breast fibroadenoma accounts for the majority of breast lumps in young women. *Boswellia* was found to exert beneficial effect against breast fibroadenomas as evinced by a study conducted by Pasta and group. They showed that treatment with the combination of *Boswellia*, betaine, and myo-inositol resulted in decreased fibroadenoma dimension in young women without exerting any toxic effects. The combination also resulted in reduced fibroadenoma volume in 38.8% of the patients in the experimental group, whereas the same was observed only in 17.85% patients in the placebo group (Pasta et al., 2016).

Cardiovascular Diseases (CVDs)

CVDs, a group of diseases which involves the heart and the blood vessels is one of the most common causes of death across the globe. Notably, guggul presents a potent remedy for cardiovascular diseases. For example, Singh and group conducted a study to evaluate the cardioprotective benefits of guggul by enrolling 200 patients suffering from ischemic heart disease. The

patients were treated with the combination of gum guggul and *Inula racemosa* for 6 months which resulted in the reduced levels of total cholesterol, triglyceride, and total blood lipids in the patients. It also restored the normal electrocardiogram (ECG) in 26% of the patients, showed improvement of ECG in 59% of the patients and lessened the chest pain in 25% of the patients (Singh et al., 1993).

Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive disease where occurs due to enhanced inflammation and oxidative stress leading to reduced kidney function. Studies have indicated *B. serrata* in combination with *Curcuma longa* as an effective regimen to obtain reduced inflammation in patients with CKD which functioned via modulation of prostaglandin E₂ (PGE₂) (Shelmadine et al., 2017). Moreover, this regimen was found to be safe, well tolerated which also enhanced the levels of inflammatory cytokines in CKD patients (Moreillon et al., 2013).

Diabetes Mellitus

A large population of the world is affected by diabetes mellitus or type 2 diabetes. Several preclinical studies have shown that the gum resin of *Commiphora* and *boswellia* are highly effective against this disease. In a clinical study conducted by Ahangarpour et al., it was observed that the treatment of patients with diabetes mellitus with *B. serrata* gum resin (900 mg daily for 6 weeks orally) resulted in decreased risk factors associated with this disease. Further, the treatment also helped in maintaining fructosamine levels, hepatic enzyme activities, and to bring lipid profiles close to normal levels in the patients (Ahangarpour et al., 2014).

Eczema and Psoriasis

Eczema, also known as dermatitis and psoriasis are caused mainly due to inflammation of the skin. *Boswellia* has been found to exert effectiveness against eczema and psoriasis. A group of scientists revealed that *Boswellia*-based cream lessens the use of topical corticosteroids and can diminish the grade of erythema and the skin superficial symptoms (Togni et al., 2015). Further, in a double blind study, the efficacy of a novel formulation of BA (Bosexil[®]) containing *B. serrata* resin extract and lecithin was evaluated against both psoriasis and eczema. Improvement in psoriasis, scales (70% of cases), and erythema (50% of cases) was observed with Bosexil[®] compared to placebo. In addition, when eczema patients were administrated with Bosexil[®] formulation, it showed improvement in both erythema (60% of cases) and itch (60% of cases) of the patients without any case of waning (Togni et al., 2014).

Fascioliasis

Fascioliasis is a parasitic worm infection caused by the common liver fluke *Fasciola hepatica* and *Fasciola gigantica*. The formulation of myrrhh, the gum resin of *Commiphora molmol* was reported to be safe, well tolerated, and effective for the management of this disease. The formulated drug comprised of 8 parts of resin and 3.5 parts of volatile oils, all extracted from myrrhh. They observed that 7 patients who were passing fasciola

TABLE 3 | Clinical trials of guggul (*Commiphora* and *Boswellia*) against various chronic diseases.

Disease	Dose	Pts (#)	Clinical outcome	References
Healthy volunteer	1 g ^b	10	Diminished efficacy	Dalvi et al., 1994
	125 mg, 2 capsules ^d	20	Increased pain threshold & tolerance force, well -tolerated	Prabhavathi et al., 2014
	140 mg ^e	47	Effective	Chilelli et al., 2016
	2 × 250 mg ^d	12	High and quick absorption	Riva et al., 2016
Asthma	900 mg/d; 6 wk ^d	40	Improved disease condition	Gupta et al., 1998
	500 mg/d ^d	32	Effective	Ferrara et al., 2015
Breast fibroadenomas	– ^e	64	Reduction in fibroadenoma mass	Pasta et al., 2016
CKD	516 mg ^e	16	Safe and tolerable	Moreillon et al., 2013
	– ^b	60	Effective	Shelmadine et al., 2017
Colitis	900 mg/d; 6 wk ^d	30	Safe and effective	Gupta et al., 2001
	1050 mg/d; 6 wk ^d	–	Effective	Gupta et al., 1997
Crohn's disease	– ^d	102	Safe and effective	Gerhardt et al., 2001
	2,400 mg/d; 52 wk ^d	108	Well-tolerated	Holtmeier et al., 2011
Fascioliasis	12 mg/kg/d; 6 d ^f	7	Safe, well-tolerated and effective	Massoud et al., 2001
	600 mg/d; 6 d ^f	1019	Safe and effective	Abo-Madyan et al., 2004b
Hepatitis C	– ^a	15	Effective	Scholtes et al., 2012
HCL	1,500 mg/d; 12 wk ^b	205	Effective	Nityanand et al., 1989
	100 mg/d; 24 wk ^f	61	Mild side effects	Singh et al., 1994
	1,000, 2,000 mg/d; 3 d ^b 103	–	Well-tolerated, caused dermatologic hypersensitivity	Szapary et al., 2003
HLD	2,160 mg/d; 12 wk ^b	43	Clinical magnitude is obscure	Nohr et al., 2009
	– ^f	–	–	Verma and Bordia, 1988
	75 mg/d; 8 wk ^a	–	Safe and effective	Beg et al., 1996
Metabolic syndrome	2 g/d; 8 wk ^b	59	Effective	Vyas et al., 2015
	2 pills/d; 4 mo ^b	78	Effective	Patti et al., 2015
Nodulocystic acne	50 mg/d; 3 mo ^b	20	Reduced inflammatory lesions	Thappa and Dogra, 1994
Osteoarthritis	2 capsules, every 8 h; 3 m-15 d wash-out-3 m ^e	42	–	Kulkarni et al., 1991
	500 mg ^b	30	Safe and effective	Singh et al., 2003
	999 mg/d; 8 wk ^d	30	Well-tolerated	Kimmatkar et al., 2003
	100 or 250 mg/d; 90 d ^d	75	Safe and effective	Sengupta et al., 2008
	1000 mg/d ^e	30	Safe and well-tolerated	Kizhakkedath, 2013
	6 capsules/d; 24 wk ^e	440	Effective, improved knee function	Chopra et al., 2013
Polyarthritis	3600 mg/d ^d	78	No measurable efficacy	Sander et al., 1998
RT-related edema	4200 mg/d ^d	44	Effective, reduced cerebral edema	Kirste et al., 2011
Schistosomiasis	10 mg/kg/d; 3d ^f	204	Well-tolerated	Sheir et al., 2001
	600 mg/d; 6 d ^f	1019	Safe and effective	Abo-Madyan et al., 2004a
Skin damage in MCA	Cream, twice/d ^d	114	Well-tolerated	Togni et al., 2015
SUI	4 g/d, 8 wk ^e	30	Effective	Arkalgud Rangaswamy et al., 2014

CKD, Chronic kidney disease; d, Day; HCL, Hypercholesterolemia; HLD, Hyperlipidemia; MCA, Mammary carcinoma; mo, Month; wk, Week; RT, Radiotherapy; SUI, Stress urinary incontinence; a, Guggulsterone; b, Guggul; c, Formulation of guggul; d, Boswellia; e, Formulation of Boswellia; f, Commiphora.

eggs in their stools displayed distinct improvement of the general condition, drop in the egg count, and improvement of all signs and symptoms with no adverse side effects after treatment with the drug (Massoud et al., 2001).

Gingivitis

Gingivitis, the inflammation of gingiva is a very common form of gum disease. Frankincense extract has been found to exhibit efficacy against gingivitis. A double blinded randomized

placebo controlled trial was conducted among 75 female patients aged between 15 and 18 years with moderate plaque-induced gingivitis. Six groups were randomly formed based on the administration of 0.1g of frankincense extract, 0.2g of its powder, placebo, and whether the patients have undergone scaling and root planning (SRP) or not. Gingival index, plaque index, bleeding index, and probing pocket depth were measured on the 0, 7th, and 14th days of the study. Detailed analysis of the data revealed that SRP along with the application of

frankincense extract or powder might cause significant decrease in inflammatory indices in comparison to the groups without drug therapy and SRP (Khosravi Samani et al., 2011).

Inflammatory Bowel Disease

Different clinical studies with guggul have shown its efficacy against IBDs which include colitis and Crohn's disease. For instance, the gum resin of *B. serrata* was found to be effective in the treatment of chronic colitis with minimal side effects in a clinical study conducted by Gupta et al. In this study, the patients with chronic colitis were treated with gum resin from *B. serrata* at a dose of 900 mg daily divided in three doses for 6 weeks. The treatment resulted in the improvement of stool properties, hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes, and eosinophils in the patients (Gupta et al., 2001). Further, a double-blind, placebo-controlled, randomized, parallel study on 82 patients with Crohn's disease was conducted where patients were given a new *B. serrata* extract; Boswelan. In this trial, remission was observed in 59.9% of the actively treated patients. Additionally, this study also confirmed better tolerability of Boswelan in long-term treatment of Crohn's disease (Holtmeier et al., 2011). Furthermore, leukotrienes play an important role in inflammation of the colon in ulcerative colitis. Sallai guggul gum resin is known to be specific, non-redox, and non-competitive inhibitors of 5-LOX, a crucial enzyme of leukotriene biosynthesis. Patients with grade II and III ulcerative colitis were treated with *B. serrata* gum resin at a dose of 350 mg thrice daily for 6 weeks. Stool properties, histopathology, and scan microscopy of rectal biopsies, blood parameters including hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes, and eosinophils showed slightly better improvement in *Boswellia* treated patients (Gupta et al., 1997).

Nodulocystic Acne

Guggulipid is considered to be very effective in topical and oral complementary as well as an alternative medicine (CAM) for the treatment of acne (Magin et al., 2006). In a clinical study conducted by Thappa and Dogra, patients with nodulocystic acne were given guggulipid equivalent to 25 mg GS for 3 months, which resulted in progressive reduction in lesions in majority of patients. However, patients with oily faces displayed better response to guggulipid (Thappa and Dogra, 1994).

Thus, these clinical studies well evince the potential effect of *Commiphora* and *Boswellia* on different chronic diseases. However, more studies are inevitable to establish them as cutting edge strategy for the treatment of diverse human diseases.

REFERENCES

- Abo-Madyan, A. A., Morsy, T. A., and Motawea, S. M. (2004a). Efficacy of Myrrh in the treatment of schistosomiasis (haematobium and mansoni) in Ezbet El-Bakly, Tamyia Center, El-Fayoum Governorate, Egypt. *J. Egypt Soc. Parasitol.* 34, 423–446.
- Abo-Madyan, A. A., Morsy, T. A., Motawea, S. M., and Morsy, A. T. (2004b). Clinical trial of Mirazid in treatment of human fascioliasis, Ezbet El-Bakly (Tamyia Center) Al-Fayoum Governorate. *J. Egypt. Soc. Parasitol.* 34, 807–818.

CONCLUSION

Since ancient times, *Commiphora* and *Boswellia* are considered as important traditional medicinal plants which are used for the treatment of various ailments. Guggul isolated from *Commiphora* and *Boswellia* have immense therapeutic potential against several diseases and it has been well established by numerous *in vitro*, *in vivo*, and clinical studies. Guggul was used traditionally for the treatment of inflammation and hyperlipidemia, but with the extensive studies on guggul and associated molecular mechanisms unveiled newer insights of its use for the treatment of various other chronic diseases as well. Gum resin guggul possesses multiple pharmacological activities especially hypolipidemic, antiobesity, anti-inflammatory, anti-tumor effects, cardioprotective, neuroprotective, hepatoprotective, thyroid stimulatory effects etc. It effectively regulates different transcription factors, enzymes, cytokines, and anti-apoptotic proteins which are involved in inflammation, carcinogenesis, and other chronic diseases. Further, *Commiphora* in combination with other ayurvedic herbs is commercially available and marketed for the treatment and cure of arthritis, obesity and associated side effects of the disease. Many patents are also filed and approved to use guggul as a constituent of polyherbal formulations and cosmetics. Therefore, taking the medicinal importance and commercial use of guggul into consideration, it can be advocated to possess substantial therapeutic potential against diverse chronic disorders. However, more *in vitro*, *in vivo*, and well-designed clinical studies are required to validate the clinical usefulness of guggul and to obtain a potent herbal derived drug with enhanced efficacy, minimal side effects and strong disease combating properties.

AUTHOR CONTRIBUTIONS

BA and AK contributed to study design and writing of the manuscript. KB and DB carried out literature survey, writing and artwork. CH, BS, and NR contributed to the making of the tables and artwork. SG and GP performed proofreading of the manuscript.

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- Agrawal, S. S., Saraswati, S., Mathur, R., and Pandey, M. (2011). Antitumor properties of Boswellic acid against Ehrlich ascites cells bearing mouse. *Food Chem. Toxicol.* 49, 1924–1934. doi: 10.1016/j.fct.2011.04.007
- Ahangarpour, A., Heidari, H., Fatemeh, R. A., Pakmehr, M., Shahbazian, H., Ahmadi, I., et al. (2014). Effect of *B. serrate* supplementation on blood lipid, hepatic enzymes and fructosamine levels in type2 diabetic patients. *J. Diabetes Metab. Disord.* 13:29. doi: 10.1186/2251-6581-13-29
- Ahn, D. W., Seo, J. K., Lee, S. H., Hwang, J. H., Lee, J. K., Ryu, J. K., et al. (2012). Enhanced antitumor effect of combination therapy with

- gemcitabine and guggulsterone in pancreatic cancer. *Pancreas* 41, 1048–1057. doi: 10.1097/MPA.0b013e318249d62e
- Ahn, S. I., and Youn, H. S. (2008). Guggulsterone suppresses the activation of NF- κ B and expression of COX-2 induced by toll-like receptor 2, 3, and 4 agonists. *Food Sci. Biotechnol.* 17, 1294–1298.
- Al-Howiriny, T. A., Al-Sohaibani, M. O., Al-Said, M. S., Al-Yahya, M. A., El-Tahir, K. H., and Rafatullah, S. (2004). Hepatoprotective properties of *Commiphora opobalsamum* (“Balessan”), a traditional medicinal plant of Saudi Arabia. *Drugs Exp. Clin. Res.* 30, 213–220. doi: 10.1055/s-0034-1382426
- Almazari, I., Park, J. M., Park, S. A., Suh, J. Y., Na, H. K., Cha, Y. N., et al. (2012). Guggulsterone induces heme oxygenase-1 expression through activation of Nrf2 in human mammary epithelial cells: PTEN as a putative target. *Carcinogenesis* 33, 368–376. doi: 10.1093/carcin/bgr259
- Ammon, H. P. (2016). Boswellic acids and their role in chronic inflammatory diseases. *Adv. Exp. Med. Biol.* 928, 291–327. doi: 10.1007/978-3-319-41334-1_13
- Ammon, H. P., Safayhi, H., Mack, T., and Sabieraj, J. (1993). Mechanism of antiinflammatory actions of curcumin and boswellic acids. *J. Ethnopharmacol.* 38, 113–119. doi: 10.1016/0378-8741(93)90005-P
- An, M. J., Cheon, J. H., Kim, S. W., Kim, E. S., Kim, T. I., and Kim, W. H. (2009). Guggulsterone induces apoptosis in colon cancer cells and inhibits tumor growth in murine colorectal cancer xenografts. *Cancer Lett.* 279, 93–100. doi: 10.1016/j.canlet.2009.01.026
- Arkalgud Rangaswamy, P., Sultana, A., Rahman, K., and Nagapattinam, S. (2014). Efficacy of *Boswellia serrata* L. and *Cyperus scariosus* L. plus pelvic floor muscle training in stress incontinence in women of reproductive age. *Complement. Ther. Clin. Pract.* 20, 230–236. doi: 10.1016/j.ctcp.2014.08.003
- Arora, R. B., Kapoor, V., Gupta, S. K., and Sharma, R. C. (1971). Isolation of a crystalline steroidal compound from *C. mukul* and its anti-inflammatory activity. *Indian J. Exp. Biol.* 9, 403–404.
- Arora, R. B., Taneja, V., Sharma, R. C., and Gupta, S. K. (1972). Anti-inflammatory studies on a crystalline steroid isolated from *C. mukul*. *Indian J. Med. Res.* 60, 929–931.
- Baldwa, V. S., Bhasin, V., Ranka, P. C., and Mathur, K. M. (1981). Effects of *C. mukul* (Guggul) in experimentally induced hyperlipemia and atherosclerosis. *J. Assoc. Phys. India* 29, 13–17.
- Banik, K., Harsha, C., Bordoloi, D., Laldhuksaki Sailo, B., Sethi, G., Leong, H. C., et al. (2018). Therapeutic potential of gambogic acid, a caged xanthone, to target cancer. *Cancer Lett.* 416, 75–86. doi: 10.1016/j.canlet.2017.12.014
- Barrett, T. Q., Kristiansen, L. H., and Ovesen, T. (2003). NF- κ B in cultivated middle ear epithelium. *Int. J. Pediatr. Otorhinolaryngol.* 67, 895–903. doi: 10.1016/S0165-5876(03)00137-X
- Batra, S., Srivastava, S., Singh, K., Chander, R., Khanna, A. K., and Bhaduri, A. P. (2000). Syntheses and biological evaluation of 3- substituted amino-1-aryl-6-hydroxy-hex-2-ene-1-ones as antioxidant and hypolipidemic agents. *Bioorg. Med. Chem.* 8, 2195–2209. doi: 10.1016/S0968-0896(00)00159-0
- Beg, M., Singhal, K. C., and Afzaal, S. (1996). A study of effect of guggulsterone on hyperlipidemia of secondary glomerulopathy. *Indian J. Physiol. Pharmacol.* 40, 237–240.
- Bhushan, S., Kumar, A., Malik, F., Andotra, S. S., Sethi, V. K., Kaur, I. P., et al. (2007). A triterpenediol from *B. serrata* induces apoptosis through both the intrinsic and extrinsic apoptotic pathways in human leukemia HL-60 cells. *Apoptosis* 12, 1911–1926. doi: 10.1007/s10495-007-0105-5
- Bordoloi, D., Roy, N. K., Monisha, J., Padmavathi, G., and Kunnumakkara, A. B. (2016). Multi-targeted agents in cancer cell chemosensitization: what we learnt from curcumin thus far. *Recent Pat. Anticancer. Drug Discov.* 11, 67–97. doi: 10.2174/1574892810666151020101706
- Büchele, B., Zugmaier, W., and Simmet, T. (2003). Analysis of pentacyclic triterpenic acids from frankincense gum resins and related phytopharmaceuticals by high-performance liquid chromatography. Identification of lupeolic acid, a novel pentacyclic triterpene. *J. Chromatogr. B.* 791, 21–30. doi: 10.1016/S1570-0232(03)00160-0
- Büchele, B., Zugmaier, W., Estrada, A., Genze, F., Syrovets, T., Paetz, C., et al. (2006). Characterization of 3 α -acetyl-11-keto- β -boswellic acid, a pentacyclic triterpenoid inducing apoptosis *in vitro* and *in vivo*. *Planta Med.* 72, 1285–1289. doi: 10.1055/s-2006-951680
- Burris, T. P., Montrose, C., Houck, K. A., Osborne, H. E., Bocchinfuso, W. P., Yaden, B. C., et al. (2005). The hypolipidemic natural product guggulsterone is a promiscuous steroid receptor ligand. *Mol. Pharmacol.* 67, 948–954. doi: 10.1124/mol.104.007054
- Chander, R., Rizvi, F., Khanna, A. K., and Pratap, R. (2003). Cardioprotective activity of synthetic guggulsterone (E and Z isomers) in isoproterenol induced myocardial ischemia in rats: a comparative study. *Indian J. Clin. Biochem.* 18, 71–79. doi: 10.1007/BF02867370
- Chashoo, G., Singh, S. K., Sharma, P. R., Mondhe, D. M., Hamid, A., Saxena, A., et al. (2011). A propionyloxy derivative of 11-keto- β -boswellic acid induces apoptosis in HL-60 cells mediated through topoisomerase I & II inhibition. *Chem. Biol. Interact.* 189, 60–71. doi: 10.1016/j.cbi.2010.10.017
- Chen, Z., Huang, C., and Ding, W. (2016). Z-guggulsterone improves the scopolamine-induced memory impairments through enhancement of the BDNF signal in C57BL/6j mice. *Neurochem. Res.* 41, 3322–3332. doi: 10.1007/s11064-016-2064-0
- Cheon, J. H., Kim, J. S., Kim, J. M., Kim, N., Jung, H. C., and Song, I. S. (2006). Plant sterol guggulsterone inhibits nuclear factor- κ B signaling in intestinal epithelial cells by blocking IkappaB kinase and ameliorates acute murine colitis. *Inflamm. Bowel Dis.* 12, 1152–1161. doi: 10.1097/01.mib.0000235830.94057.c6
- Chilelli, N. C., Ragazzi, E., Valentini, R., Cosma, C., Ferrareso, S., Lapolla, A., and Sartore, G. (2016). Curcumin and *Boswellia serrata* modulate the glyco-oxidative status and lipo-oxidation in master athletes. *Nutrients* 8:E745. doi: 10.3390/nu8110745
- Chopra, A., Saluja, M., Tillu, G., Sarmukkaddam, S., Venugopalan, A., Narsimulu, G., et al. (2013). Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis: a randomized, double-blind, controlled equivalence drug trial. *Rheumatology* 52, 1408–1417. doi: 10.1093/rheumatology/kes414
- Choudhuri, R., Degraff, W., Gamson, J., Mitchell, J. B., and Cook, J. A. (2011). Guggulsterone-mediated enhancement of radiosensitivity in human tumor cell lines. *Front. Oncol.* 1:19. doi: 10.3389/fonc.2011.00019
- Cuaz-Pérolin, C., Billiet, L., Bauge, E., Copin, C., Scott-Algara, D., Genze, F., et al. (2008). Antiinflammatory and antiatherogenic effects of the NF- κ B inhibitor acetyl-11-keto- β -boswellic acid in LPS-challenged ApoE^{-/-} mice. *Arterioscler. Thromb. Vasc. Biol.* 28, 272–277. doi: 10.1161/ATVBAHA.107.155606
- Cui, J., Huang, L., Zhao, A., Lew, J. L., Yu, J., Sahoo, S., et al. (2003). Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump. *J. Biol. Chem.* 278, 10214–10220. doi: 10.1074/jbc.M209323200
- Dalvi, S. S., Nayak, V. K., Pohujani, S. M., Desai, N. K., Kshirsagar, N. A., and Gupta, K. C. (1994). Effect of guggulipid on bioavailability of diltiazem and propranolol. *J. Assoc. Physicians India* 42, 454–455.
- De Gottardi, A., Dumonceau, J. M., Bruttin, F., Vonlaufen, A., Morard, I., Spahr, L., et al. (2006). Expression of the bile acid receptor FXR in Barrett’s esophagus and enhancement of apoptosis by guggulsterone *in vitro*. *Mol. Cancer* 5:48. doi: 10.1186/1476-4598-5-48
- Deng, R. (2007). Therapeutic effects of guggul and its constituent guggulsterone: cardiovascular benefits. *Cardiovasc. Drug Rev.* 25, 375–390. doi: 10.1111/j.1527-3466.2007.00023.x
- Dhaneshwar, S., Dipmala, P., Abhay, H., and Prashant, B. (2013). Disease-modifying effect of anthraquinone prodrug with boswellic acid on collagenase-induced osteoarthritis in Wistar rats. *Inflamm. Allergy Drug Targets* 12, 288–295. doi: 10.2174/18715281113129990002
- Ding, Y., Chen, M., Wang, M., Li, Y., and Wen, A. (2015). Posttreatment with 11-Keto- β -boswellic acid ameliorates cerebral ischemia-reperfusion injury: Nrf2/HO-1 pathway as a potential mechanism. *Mol. Neurobiol.* 52, 1430–1439. doi: 10.1007/s12035-014-8929-9
- Ding, Y., Chen, M., Wang, M., Wang, M., Zhang, T., Park, J., et al. (2014). Neuroprotection by acetyl-11-keto- β -Boswellic acid, in ischemic brain injury involves the Nrf2/HO-1 defense pathway. *Sci. Rep.* 4:7002. doi: 10.1038/srep07002
- Dixit, D., Ghildiyal, R., Anto, N. P., Ghosh, S., Sharma, V., and Sen, E. (2013). Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras/NF κ B dependent manner. *Cancer Lett.* 336, 347–358. doi: 10.1016/j.canlet.2013.03.025
- Dixit, V. P., Joshi, S., Sinha, R., Bharvava, S. K., and Varma, M. (1980). Hypolipidemic activity of guggal resin (*C. mukul*) and garlic (*Alium sativum*

- linn.) in dogs (*Canis familiaris*) and monkeys (*Presbytis entellus entellus* Dufresne). *Biochem. Exp. Biol.* 16, 421–424.
- Du, Z., Liu, Z., Ning, Z., Liu, Y., Song, Z., Wang, C., et al. (2015). Prospects of boswellic acids as potential pharmaceuticals. *Planta Med.* 81, 259–271. doi: 10.1055/s-0034-1396313
- Fan, A. Y., Lao, L., Zhang, R. X., Zhou, A. N., Wang, L. B., Moudgil, K. D., et al. (2005). Effects of an acetone extract of *B. carterii* Birdw. (Burseraceae) gum resin on adjuvant-induced arthritis in lewis rats. *J. Ethnopharmacol.* 101, 104–109. doi: 10.1016/j.jep.2005.03.033
- Ferrara, T., De Vincentiis, G., and Di Pierro, F. (2015). Functional study on *Boswellia* phytosome as complementary intervention in asthmatic patients. *Eur. Rev. Med. Pharmacol. Sci.* 19, 3757–3762.
- Francis, J. A., Raja, S. N., and Nair, M. G. (2004). Bioactive terpenoids and guggulsteroids from *C. mukul* gum resin of potential anti-inflammatory interest. *Chem. Biodiversity* 1, 1842–1853. doi: 10.1002/cbdv.200490138
- Frank, M. B., Yang, Q., Osban, J., Azzarello, J. T., Saban, M. R., Saban, R., et al. (2009). Frankincense oil derived from *Boswellia carteri* induces tumor cell specific cytotoxicity. *BMC Complement. Altern. Med.* 9:6. doi: 10.1186/1472-6882-9-6
- Gerhardt, H., Seifert, F., Buvari, P., Vogelsang, H., and Regges, R. (2001). Therapy of active Crohn disease with *Boswellia serrata* extract H 15. *Z. Gastroenterol.* 39, 11–17. doi: 10.1055/s-2001-10708
- Glaser, T., Winter, S., Groscurth, P., Safayhi, H., Sailer, E. R., Ammon, H. P., et al. (1999). Boswellic acids and malignant glioma: induction of apoptosis but no modulation of drug sensitivity. *Br. J. Cancer.* 80, 756–765. doi: 10.1038/sj.bjc.6690419
- Guan, B., Hoque, A., and Xu, X. (2014). Amiloride and guggulsterone suppression of esophageal cancer cell growth *in vitro* and in nude mouse xenografts. *Front. Biol.* 9, 75–81. doi: 10.1007/s11515-014-1289-z
- Guan, B., Li, H., Yang, Z., Hoque, A., and Xu, X. (2013). Inhibition of farnesoid X receptor controls esophageal cancer cell growth *in vitro* and in nude mouse xenografts. *Cancer* 119, 1321–1329. doi: 10.1002/cncr.27910
- Gupta, I., Gupta, V., Parihar, A., Gupta, S., Lüdtke, R., Safayhi, H., et al. (1998). Effects of *B. serrata* gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur. J. Med. Res.* 3, 511–514.
- Gupta, I., Parihar, A., Malhotra, P., Gupta, S., Lüdtke, R., Safayhi, H., et al. (2001). Effects of gum resin of *B. serrata* in patients with chronic colitis. *Planta Med.* 67, 391–395. doi: 10.1055/s-2001-15802
- Gupta, I., Parihar, A., Malhotra, P., Singh, G. B., Lüdtke, R., Safayhi, H., et al. (1997). Effects of *B. serrata* gum resin in patients with ulcerative colitis. *Eur. J. Med. Res.* 2, 37–43.
- Hanus, L. O., Reznicka, T., Dembitsky, V. M., and Moussaieff, A. (2005). Myrrh-*commiphora* chemistry. *Biomed. Papers* 149, 3–28. doi: 10.5507/bp.2005.001
- Harsha, C., Banik, K., Bordoloi, D., and Kunnumakkara, A. B. (2017). Antiulcer properties of fruits and vegetables: a mechanism based perspective. *Food Chem. Toxicol.* 108, 104–119. doi: 10.1016/j.fct.2017.07.023
- Hazra, A. K., Sur, T. K., Chakraborty, B., and Seal, T. (2018). HPLC analysis of phenolic acids and antioxidant activity of some classical ayurvedic guggulu formulations. *Int. J. Res. Ayurveda Pharm.* 9, 112–117. doi: 10.7897/2277-4343.09122
- Hoernlein, R. F., Orlikowsky, T. H., Zehrer, C., Niethammer, D., Sailer, E. R., Simmet, T., et al. (1999). Acetyl-11-keto-beta-boswellic acid induces apoptosis in HL-60 and CCRF-CEM cells and inhibits topoisomerase I. *J. Pharmacol. Exp. Ther.* 288, 613–619.
- Holtmeier, W., Zeuzem, S., Preiss, J., Kruis, W., Böhm, S., Maaser, C., et al. (2011). Randomized, placebo-controlled, double-blind trial of *B. serrata* in maintaining remission of Crohn's disease: good safety profile but lack of efficacy. *Inflamm. Bowel Dis.* 17, 573–582. doi: 10.1002/ibd.21345
- Hostanska, K., Daum, G., and Saller, R. (2002). Cytostatic and apoptosis-inducing activity of boswellic acids toward malignant cell lines *in vitro*. *Anticancer Res.* 22, 2853–2862.
- Huang, C., Wang, J., Lu, X., Hu, W., Wu, F., Jiang, B., et al. (2016). Z-guggulsterone negatively controls microglia-mediated neuroinflammation via blocking I κ B- α -NF- κ B signals. *Neurosci. Lett.* 619, 34–42. doi: 10.1016/j.neulet.2016.02.021
- Huang, M. T., Badmaev, V., Ding, Y., Liu, Y., Xie, J. G., and Ho, C. T. (2000). Anti-tumor and anti-carcinogenic activities of triterpenoid, beta-boswellic acid. *Biofactors* 13, 225–230. doi: 10.1002/biof.5520130135
- Ichikawa, H., and Aggarwal, B. B. (2006). Guggulsterone inhibits osteoclastogenesis induced by receptor activator of nuclear factor-kappaB ligand and by tumor cells by suppressing nuclear factor-kappaB activation. *Clin. Cancer Res.* 12, 662–668. doi: 10.1158/1078-0432.CCR-05-1749
- Jiang, G., Xiao, X., Zeng, Y., Nagabhushanam, K., Majeed, M., and Xiao, D. (2013). Targeting beta-catenin signaling to induce apoptosis in human breast cancer cells by z-guggulsterone and Gugulipid extract of Ayurvedic medicine plant *Commiphora mukul*. *BMC Complement. Altern. Med.* 13:203. doi: 10.1186/1472-6882-13-203
- Jing, Y., Nakajo, S., Xia, L., Nakaya, K., Fang, Q., Waxman, S., et al. (1999). Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. *Leuk. Res.* 23, 43–50. doi: 10.1016/S0145-2126(98)00096-4
- Kalariya, N. M., Shoeb, M., Reddy, A. B., Zhang, M., Van Kuijk, F. J., and Ramana, K. V. (2010). Prevention of endotoxin-induced uveitis in rats by plant sterol guggulsterone. *Invest. Ophthalmol. Vis. Sci.* 51, 5105–5113. doi: 10.1167/iov.09-4873
- Kang, S. J., Kim, J. M., Koh, S. J., Kim, S. H., Im, J. P., Jung, H. C., et al. (2013). The guggulsterone derivative GG-52 inhibits NF- κ B signaling in bone marrow-derived dendritic cells and attenuates colitis in IL-10 knockout mice. *Life Sci.* 92, 1064–1071. doi: 10.1016/j.lfs.2013.04.003
- Kaul, S., and Kapoor, N. K. (1989). Reversal of changes of lipid peroxide, xanthine oxidase and superoxide dismutase by cardio-protective drugs in isoproterenol induced myocardial necrosis in rats. *Indian. J. Exp. Biol.* 27, 625–627.
- Khan, M. K., Ansari, I. A., and Khan, M. S. (2013). Dietary phytochemicals as potent chemotherapeutic agents against breast cancer: inhibition of NF-kappaB pathway via molecular interactions in rel homology domain of its precursor protein p105. *Pharmacogn. Mag.* 9, 51–57. doi: 10.4103/0973-1296.108140
- Khan, S., Kaur, R., Shah, B. A., Malik, F., Kumar, A., Bhushan, S., et al. (2012). A novel cyano derivative of 11-keto- β -boswellic acid causes apoptotic death by disrupting PI3K/AKT/Hsp-90 cascade, mitochondrial integrity, and other cell survival signaling events in HL-60 cells. *Mol. Carcinog.* 51, 679–695. doi: 10.1002/mc.20821
- Khanna, D. S., Agarwal, O. P., Gupta, S. K., and Arora, R. B. (1969). A biochemical approach to anti-atherosclerotic action of *Commiphora-mukul*: an Indian indigenous drug in Indian domestic pigs (*Sus scrofa*). *Indian J. Med. Res.* 57, 900–906.
- Khosravi Samani, M., Mahmoodian, H., Moghadamnia, A., Poorsattar Bejeh Mir, A., and Chitsazan, M. (2011). The effect of Frankincense in the treatment of moderate plaque-induced gingivitis: a double blinded randomized clinical trial. *Daru* 19, 288–294.
- Kim, B. H., Yoon, J. H., Yang, J. I., Myung, S. J., Lee, J. H., Jung, E. U., et al. (2013). Guggulsterone attenuates activation and survival of hepatic stellate cell by inhibiting nuclear factor kappa B activation and inducing apoptosis. *J. Gastroenterol. Hepatol.* 28, 1859–1868. doi: 10.1111/jgh.12314
- Kim, D. G., Bae, G. S., Choi, S. B., Jo, I. J., Shin, J. Y., Lee, S. K., et al. (2015). Guggulsterone attenuates cerulein-induced acute pancreatitis via inhibition of ERK and JNK activation. *Int. Immunopharmacol.* 26, 194–202. doi: 10.1016/j.intimp.2015.03.030
- Kim, D. G., Bae, G. S., Jo, I. J., Choi, S. B., Kim, M. J., Jeong, J. H., et al. (2016). Guggulsterone attenuated lipopolysaccharide-induced inflammatory responses in mouse inner medullary collecting duct-3 cells. *Inflammation* 39, 87–95. doi: 10.1007/s10753-015-0226-x
- Kim, E. S., Hong, S. Y., Lee, H. K., Kim, S. W., An, M. J., Kim, T. I., et al. (2008). Guggulsterone inhibits angiogenesis by blocking STAT3 and VEGF expression in colon cancer cells. *Oncol. Rep.* 20, 1321–1327. doi: 10.3892/or_00000147
- Kim, J. M., Kang, H. W., Cha, M. Y., Yoo, D., Kim, N., Kim, I. K., et al. (2010). Novel guggulsterone derivative GG-52 inhibits NF-kappaB signaling in intestinal epithelial cells and attenuates acute murine colitis. *Lab. Invest.* 90, 1004–1015. doi: 10.1038/labinvest.2010.54
- Kim, N., Park, J. M., Lee, S. H., Kim, B. H., Son, J. H., Ryu, J. K., et al. (2017). Effect of combinatory treatment with resveratrol and guggulsterone on mild acute pancreatitis in mice. *Pancreas* 46, 366–371. doi: 10.1097/MPA.0000000000000763
- Kimmatkar, N., Thawani, V., Hingorani, L., and Khiyani, R. (2003). Efficacy and tolerability of *B. serrata* extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. *Phytomedicine* 10, 3–7. doi: 10.1078/094471103321648593

- Kimura, I., Yoshikawa, M., Kobayashi, S., Sugihara, Y., Suzuki, M., Oominami, H., et al. (2001). New triterpenes, myrrhanol A and myrrhanone A, from guggul-gum resins, and their potent antiinflammatory effect on adjuvant-induced air-pouch granuloma of mice. *Bioorg. Med. Chem. Lett.* 11, 985–989. doi: 10.1016/S0960-894X(01)00111-1
- Kinne, R. W., Stuhlmueller, B., and Burmester, G. R. (2007). Cells of the synovium in rheumatoid arthritis Macrophages. *Arthritis Res. Ther.* 9:224. doi: 10.1186/ar2333
- Kirste, S., Treier, M., Wehrle, S. J., Becker, G., Abdel-Tawab, M., Gerbeth, K., et al. (2011). *Boswellia serrata* acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. *Cancer* 117, 3788–3795. doi: 10.1002/cncr.25945
- Kizhakkeedath, R. (2013). Clinical evaluation of a formulation containing *Curcuma longa* and *Boswellia serrata* extracts in the management of knee osteoarthritis. *Mol. Med. Rep.* 8, 1542–1548. doi: 10.3892/mmr.2013.1661
- Kong, J. N., He, Q., Wang, G., Dasgupta, S., Dinkins, M. B., Zhu, G., et al. (2015). Guggulsterone and bexarotene induce secretion of exosome-associated breast cancer resistance protein and reduce doxorubicin resistance in MDA-MB-231 cells. *Int. J. Cancer* 137, 1610–1620. doi: 10.1002/ijc.29542
- Koo, J. H., Rhee, K. S., Koh, H. W., Jang, H. Y., Park, B. H., and Park, J. W. (2012). Guggulsterone inhibits melanogenesis in B16 murine melanoma cells by downregulating tyrosinase expression. *Int. J. Mol. Med.* 30, 974–978. doi: 10.3892/ijmm.2012.1057
- Kriegelstein, C. F., Anthoni, C., Rijcken, E. J., Laukötter, M., Spiegel, H. U., Boden, S. E., et al. (2001). Acetyl-11-keto-beta-boswellic acid, a constituent of a herbal medicine from *Boswellia serrata* resin, attenuates experimental ileitis. *Int. J. Colorectal Dis.* 16, 88–95. doi: 10.1007/s003840100292
- Kulkarni, R. R., Patki, P. S., Jog, V. P., Gandage, S. G., and Patwardhan, B. (1991). Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. *J. Ethnopharmacol.* 33, 91–95. doi: 10.1016/0378-8741(91)90167-C
- Kunnumakkara, A. B., Bordoloi, D., Harsha, C., Banik, K., Gupta, S. C., and Aggarwal, B. B. (2017). Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. *Clin. Sci.* 131, 1781–1799. doi: 10.1042/CS20160935
- Kunnumakkara, A. B., Nair, A. S., Sung, B., Pandey, M. K., and Aggarwal, B. B. (2009). Boswellic acid blocks signal transducers and activators of transcription 3 signaling, proliferation, and survival of multiple myeloma via the protein tyrosine phosphatase SHP-1. *Mol. Cancer Res.* 7, 118–128. doi: 10.1158/1541-7786.MCR-08-0154
- Kunnumakkara, A. B., Sailo, B. L., Banik, K., Harsha, C., Prasad, S., Gupta, S. C., et al. (2018). Chronic diseases, inflammation, and spices: how are they linked? *J. Transl. Med.* 16:14. doi: 10.1186/s12967-018-1381-2
- Lata, S., Saxena, K. K., Bhasin, V., Saxena, R. S., Kumar, A., and Srivastava, V. K. (1991). Beneficial effects of *Allium sativum*, *Allium cepa* and *C. mukul* on experimental hyperlipidemia and atherosclerosis—a comparative evaluation. *J. Postgrad. Med.* 37, 132–135.
- Lee, D., Kim, T., Kim, K. H., Ham, J., Jang, T. S., Kang, K. S., et al. (2017). Evaluation of guggulsterone derivatives as novel kidney cell protective agents against cisplatin-induced nephrotoxicity. *Bioorg. Med. Chem. Lett.* 27, 3156–3161. doi: 10.1016/j.bmcl.2017.05.033
- Lee, Y. R., Lee, J. H., Noh, E. M., Kim, E. K., Song, M. Y., Jung, W. S., et al. (2008). Guggulsterone blocks IL-1beta-mediated inflammatory responses by suppressing NF-kappaB activation in fibroblast-like synoviocytes. *Life Sci.* 82, 1203–1209. doi: 10.1016/j.lfs.2008.04.006
- Leeman-Neill, R. J., Wheeler, S. E., Singh, S. V., Thomas, S. M., Seethala, R. R., Neill, D. B., et al. (2009). Guggulsterone enhances head and neck cancer therapies via inhibition of signal transducer and activator of transcription-3. *Carcinogenesis* 30, 1848–1856. doi: 10.1093/carcin/bgp211
- Li, C., Zang, Y., Sen, M., Leeman-Neill, R. J., Man, D. S., Grandis, J. R., et al. (2009). Bortezomib up-regulates activated signal transducer and activator of transcription-3 and synergizes with inhibitors of signal transducer and activator of transcription 3 to promote head and neck squamous cell carcinoma cell death. *Mol. Cancer Ther.* 8, 2211–2220. doi: 10.1158/1535-7163.MCT-09-0327
- Liu, F. G., Hu, W. F., Wang, J. L., Wang, P., Gong, Y., Tong, L. J., et al. (2017). Z-guggulsterone produces antidepressant-like effects in mice through activation of the BDNF signaling pathway. *Int. J. Neuropsychopharmacol.* 20, 485–497. doi: 10.1093/ijnp/pyx009
- Liu, H. P., Gao, Z. H., Cui, S. X., Wang, Y., Li, B. Y., Lou, H. X., et al. (2013). Chemoprevention of intestinal adenomatous polyposis by acetyl-11-keto-beta-boswellic acid in APC(Min/+) mice. *Int. J. Cancer* 132, 2667–2681. doi: 10.1002/ijc.27929
- Liu, J. J., Huang, B., and Hooi, S. C. (2006). Acetyl-keto-beta-boswellic acid inhibits cellular proliferation through a p21-dependent pathway in colon cancer cells. *Br. J. Pharmacol.* 148, 1099–1107. doi: 10.1038/sj.bjp.0706817
- Liu, J. J., Nilsson, A., Oredsson, S., Badmaev, V., and Duan, R. D. (2002a). Keto- and acetyl-keto-boswellic acids inhibit proliferation and induce apoptosis in Hep G2 cells via a caspase-8 dependent pathway. *Int. J. Mol. Med.* 10, 501–505. doi: 10.3892/ijmm.10.4.501
- Liu, J. J., Nilsson, A., Oredsson, S., Badmaev, V., Zhao, W. Z., and Duan, R. D. (2002b). Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent on Fas/Fas ligand interaction in colon cancer HT-29 cells. *Carcinogenesis* 23, 2087–2093. doi: 10.1093/carcin/23.12.2087
- Liu, Z., Liu, X., Sang, L., Liu, H., Xu, Q., and Liu, Z. (2015). Boswellic acid attenuates asthma phenotypes by downregulation of GATA3 via pSTAT6 inhibition in a murine model of asthma. *Int. J. Clin. Exp. Pathol.* 8, 236–243.
- Lu, M., Xia, L., Hua, H., and Jing, Y. (2008). Acetyl-keto-beta-boswellic acid induces apoptosis through a death receptor 5-mediated pathway in prostate cancer cells. *Cancer Res.* 68, 1180–1186. doi: 10.1158/0008-5472.CAN-07-2978
- Macha, M. A., Matta, A., Chauhan, S. S., Siu, K. W., and Ralhan, R. (2011a). Guggulsterone (GS) inhibits smokeless tobacco and nicotine-induced NF-κB and STAT3 pathways in head and neck cancer cells. *Carcinogenesis* 32, 368–380. doi: 10.1093/carcin/bgq278
- Macha, M. A., Matta, A., Chauhan, S., Siu, K. M., and Ralhan, R. (2010). 14-3-3 zeta is a molecular target in guggulsterone induced apoptosis in head and neck cancer cells. *BMC Cancer* 10:655. doi: 10.1186/1471-2407-10-655
- Macha, M. A., Matta, A., Chauhan, S., Siu, K. M., and Ralhan, R. (2011b). Guggulsterone targets smokeless tobacco induced PI3K/Akt pathway in head and neck cancer cells. *PLoS ONE* 6:e14728. doi: 10.1371/journal.pone.0014728
- Macha, M. A., Rachagani, S., Gupta, S., Pai, P., Ponnusamy, M. P., Batra, S. K., et al. (2013). Guggulsterone decreases proliferation and metastatic behavior of pancreatic cancer cells by modulating JAK/STAT and Src/FAK signaling. *Cancer Lett.* 341, 166–177. doi: 10.1016/j.canlet.2013.07.037
- Magin, P. J., Adams, J., Pond, C. D., and Smith, W. (2006). Topical and oral CAM in acne: a review of the empirical evidence and a consideration of its context. *Complement. Ther. Med.* 14, 62–76. doi: 10.1016/j.ctim.2005.10.007
- Mahesh, B. U., Shrivastava, S., Pragada, R. R., Naidu, V. G., and Sistla, R. (2014). Antioxidant and hepatoprotective effects of *Boswellia ovalifoliolata* bark extracts. *Chin. J. Nat. Med.* 12, 663–671. doi: 10.1016/S1875-5364(14)60101-1
- Massoud, A., El Sisi, S., Salama, O., and Massoud, A. (2001). Preliminary study of therapeutic efficacy of a new fasciolocidal drug derived from *Commiphora molmol* (myrrh). *Am. J. Trop. Med. Hyg.* 65, 96–99. doi: 10.4269/ajtmh.2001.65.96
- Mencarelli, A., Renga, B., Palladino, G., Distrutti, E., and Fiorucci, S. (2009). The plant sterol guggulsterone attenuates inflammation and immune dysfunction in murine models of inflammatory bowel disease. *Biochem. Pharmacol.* 78, 1214–1223. doi: 10.1016/j.bcp.2009.06.026
- Meselhy, M. R. (2003). Inhibition of LPS-induced NO production by the oleogum resin of *Commiphora wightii* and its constituents. *Phytochemistry* 62, 213–218. doi: 10.1016/S0031-9422(02)00388-6
- Meyer, U., Costantino, G., Macchiarulo, A., and Pellicciari, R. (2005). Is antagonism of E/Z-guggulsterone at the farnesoid X receptor mediated by a noncanonical binding site? A molecular modeling study. *J. Med. Chem.* 48, 6948–6955. doi: 10.1021/jm0505056
- Moon, D. O., Park, S. Y., Choi, Y. H., Ahn, J. S., and Kim, G. Y. (2011). Guggulsterone sensitizes hepatoma cells to TRAIL-induced apoptosis through the induction of CHOP-dependent DR5: involvement of ROS-dependent ER-stress. *Biochem. Pharmacol.* 82, 1641–1650. doi: 10.1016/j.bcp.2011.08.019
- Morad, S. A., Schmid, M., Buchele, B., Siehl, H. U., El Gafaary, M., Lunov, O., et al. (2013). A novel semisynthetic inhibitor of the FRB domain of mammalian target of rapamycin blocks proliferation and triggers apoptosis in chemoresistant prostate cancer cells. *Mol. Pharmacol.* 83, 531–541. doi: 10.1124/mol.112.081349
- Moreillon, J. J., Bowden, R. G., Deike, E., Griggs, J., Wilson, R., Shelmadine, B., et al. (2013). The use of an anti-inflammatory supplement in patients

- with chronic kidney disease. *J. Complement Integr. Med.* 10, 143–152. doi: 10.1515/jcim-2012-0011
- Nabekura, T., Yamaki, T., Ueno, K., and Kitagawa, S. (2008). Inhibition of P-glycoprotein and multidrug resistance protein 1 by dietary phytochemicals. *Cancer Chemother. Pharmacol.* 62, 867–873. doi: 10.1007/s00280-007-0676-4
- Nityanand, S., Srivastava, J. S., and Asthana, O. P. (1989). Clinical trials with guggulipid. A new hypolipidaemic agent. *J. Assoc. Physicians India* 37, 323–328.
- Nohr, L. A., Rasmussen, L. B., and Straand, J. (2009). Resin from the mukul myrrh tree, guggul, can it be used for treating hypercholesterolemia? A randomized, controlled study. *Complement. Ther. Med.* 17, 16–22. doi: 10.1016/j.ctim.2008.07.001
- Ojha, S., Bhatia, J., Arora, S., Golechha, M., Kumari, S., and Arya, D. S. (2011). Cardioprotective effects of *C. mukul* against isoprenaline-induced cardiotoxicity: a biochemical and histopathological evaluation. *J. Environ. Biol.* 32, 731–738.
- Ovesen, T., and Ledet, T. (1992). Bacteria and endotoxin in middle ear fluid and the course of secretory otitis media. *Clin. Otolaryngol. Allied Sci.* 17, 531–534. doi: 10.1111/j.1365-2273.1992.tb01713.x
- Owsley, E., and Chiang, J. Y. (2003). Guggulsterone antagonizes farnesoid X receptor induction of bile salt export pump but activates pregnane X receptor to inhibit cholesterol 7 α -hydroxylase gene. *Biochem. Biophys. Res. Commun.* 304, 191–195. doi: 10.1016/S0006-291X(03)00551-5
- Panda, S., and Kar, A. (2005). Guggulu (*C. mukul*) potentially ameliorates hypothyroidism in female mice. *Phytother. Res.* 19, 78–80. doi: 10.1002/ptr.1602
- Pang, X., Yi, Z., Zhang, X., Sung, B., Qu, W., Lian, X., et al. (2009). Acetyl-11-keto-beta-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. *Cancer Res.* 69, 5893–5900. doi: 10.1158/0008-5472.CAN-09-0755
- Park, B., Prasad, S., Yadav, V., Sung, B., and Aggarwal, B. B. (2011a). Boswellic acid suppresses growth and metastasis of human pancreatic tumors in an orthotopic nude mouse model through modulation of multiple targets. *PLoS ONE* 6:e26943. doi: 10.1371/journal.pone.0026943
- Park, B., Sung, B., Yadav, V. R., Cho, S. G., Liu, M., and Aggarwal, B. B. (2011b). Acetyl-11-keto- β -boswellic acid suppresses invasion of pancreatic cancer cells through the downregulation of CXCR4 chemokine receptor expression. *Int. J. Cancer* 129, 23–33. doi: 10.1002/ijc.25966
- Park, Y. S., Lee, J. H., Bondar, J., Harwalkar, J. A., Safayhi, H., and Golubic, M. (2002a). Cytotoxic action of acetyl-11-keto-beta-boswellic acid (AKBA) on meningioma cells. *Planta Med.* 68, 397–401. doi: 10.1055/s-2002-32090
- Park, Y. S., Lee, J. H., Harwalkar, J. A., Bondar, J., Safayhi, H., and Golubic, M. (2002b). Acetyl-11-keto-beta-boswellic acid (AKBA) is cytotoxic for meningioma cells and inhibits phosphorylation of the extracellular-signal regulated kinase 1 and 2. *Adv. Exp. Med. Biol.* 507, 387–393. doi: 10.1007/978-1-4615-0193-0_60
- Pasta, V., Dinicola, S., Giuliani, A., Harrath, A. H., Alwasel, S. H., Tartaglia, F., et al. (2016). A randomized trial of *Boswellia* in association with betaine and myoinositol in the management of breast fibroadenomas. *Eur. Rev. Med. Pharmacol. Sci.* 20, 1860–1865.
- Pathania, A. S., Wani, Z. A., Guru, S. K., Kumar, S., Bhushan, S., Korkaya, H., et al. (2015). The anti-angiogenic and cytotoxic effects of the boswellic acid analog BA145 are potentiated by autophagy inhibitors. *Mol. Cancer.* 14:6. doi: 10.1186/1476-4598-14-6
- Patti, A. M., Al-Rasadi, K., Katsiki, N., Banerjee, Y., Nikolic, D., Vanella, L., et al. (2015). Effect of a natural supplement containing *Curcuma longa*, guggul, and chlorogenic acid in patients with metabolic syndrome. *Angiology* 66, 856–861. doi: 10.1177/0003319714568792
- Prabhavathi, K., Chandra, U. S., Soanker, R., and Rani, P. U. (2014). A randomized, double blind, placebo controlled, cross over study to evaluate the analgesic activity of *Boswellia serrata* in healthy volunteers using mechanical pain model. *Indian J. Pharmacol.* 46, 475–479. doi: 10.4103/0253-7613.140570
- Qurishi, Y., Hamid, A., Sharma, P. R., Wani, Z. A., Mondhe, D. M., Singh, S. K., et al. (2012). PARP cleavage and perturbation in mitochondrial membrane potential by 3- α -propionyloxy- β -boswellic acid results in cancer cell death and tumor regression in murine models. *Future Oncol.* 8, 867–881. doi: 10.2217/fon.12.68
- Qurishi, Y., Hamid, A., Sharma, P. R., Wani, Z. A., Mondhe, D. M., Singh, S. K., et al. (2013). NF- κ B down-regulation and PARP cleavage by novel 3- α -butyryloxy- β -boswellic acid results in cancer cell specific apoptosis and *in vivo* tumor regression. *Anticancer. Agents Med. Chem.* 13, 777–790. doi: 10.2174/1871520611313050012
- Ravanan, P., Singh, S. K., Rao, G. S., and Kondaiah, P. (2011). Growth inhibitory, apoptotic and anti-inflammatory activities displayed by a novel modified triterpenoid, cyano enone of methyl boswellates. *J. Biosci.* 36, 297–307. doi: 10.1007/s12038-011-9056-7
- Reddy, G. K., and Dhar, S. C. (1987). Effect of a new non-steroidal anti-inflammatory agent on lysosomal stability in adjuvant induced arthritis. *Ital. J. Biochem.* 36, 205–217.
- Riva, A., Morazzoni, P., Artariam, C., Allegrini, P., Meinsm, J., Savio Appendino, G., et al. (2016). A single-dose, randomized, cross-over, two-way, open-label study for comparing the absorption of boswellic acids and its lecithin formulation. *Phytomedicine* 23, 1375–1382. doi: 10.1016/j.phymed.2016.07.009
- Rizzo, G., Disante, M., Mencarelli, A., Renga, B., Gioiello, A., Pellicciari, R., et al. (2006). The farnesoid X receptor promotes adipocyte differentiation and regulates adipose cell function *in vivo*. *Mol. Pharmacol.* 70, 1164–1173. doi: 10.1124/mol.106.023820
- Roy, N. K., Deka, A., Bordoloi, D., Mishra, S., Kumar, A. P., Sethi, G., et al. (2016). The potential role of boswellic acids in cancer prevention and treatment. *Cancer Lett.* 377, 74–86. doi: 10.1016/j.canlet.2016.04.017
- Safayhi, H., Mack, T., Sabieraj, J., Anazodo, M. I., Subramanian, L. R., and Ammon, H. P. (1992). Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. *J. Pharmacol. Exp. Ther.* 261, 1143–1146.
- Safayhi, H., Rall, B., Sailer, E. R., and Ammon, H. P. (1997). Inhibition by boswellic acids of human leukocyte elastase. *J. Pharmacol. Exp. Ther.* 281, 460–463.
- Safayhi, H., Sailer, E. R., and Ammon, H. P. (1995). Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-beta-boswellic acid. *Mol. Pharmacol.* 47, 1212–1216.
- Samudio, I., Konopleva, M., Safe, S., McQueen, T., and Andreeff, M. (2005). Guggulsterones induce apoptosis and differentiation in acute myeloid leukemia: identification of isomer-specific antileukemic activities of the pregnadienedione structure. *Mol. Cancer Ther.* 4, 1982–1992. doi: 10.1158/1535-7163.MCT-05-0247
- Sander, O., Herborn, G., and Rau, R. (1998). Is H15 (resin extract of *Boswellia serrata*, “incense”) a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study. *Z. Rheumatol.* 57, 11–16. doi: 10.1007/s003930050051
- Sarup, P., Bala, S., and Kamboj, S. (2015). Pharmacology and Phytochemistry of Oleo-Gum Resin of *Commiphora wightii* (Guggulu). *Scientifica* 2015:138039. doi: 10.1155/2015/138039
- Satyavati, G. V., Dwarakanath, C., and Tripathi, S. N. (1969). Experimental studies on the hypocholesterolemic effect of *C. mukul* Engl. (Guggul). *Indian J. Med. Res.* 57, 1950–1962.
- Saxena, G., Singh, S. P., Pal, R., Singh, S., Pratap, R., and Nath, C. (2007). Guggulipid, an extract of *Commiphora whightii* with lipid-lowering properties, has protective effects against streptozotocin-induced memory deficits in mice. *Pharmacol. Biochem. Behav.* 86, 797–805. doi: 10.1016/j.pbb.2007.03.010
- Scholtes, C., André, P., Trépo, C., Cornu, C., Remontet, L., Ecochard, R., et al. (2012). Farnesoid X receptor targeting for hepatitis C: study protocol for a proof-of-concept trial. *Therapie* 67, 423–427. doi: 10.2515/therapie/2012058
- Sengupta, K., Alluri, K. V., Satish, A. R., Mishra, S., Golakoti, T., Sarma, K. V., et al. (2008). A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. *Arthritis Res. Ther.* 10:R85. doi: 10.1186/ar2461
- Shah, R., Gulati, V., and Palombo, E. A. (2012). Pharmacological properties of guggulsterones, the major active components of gum guggul. *Phytother. Res.* 26, 1594–1605. doi: 10.1002/ptr.4647
- Shao, Y., Ho, C. T., Chin, C. K., Badmaev, V., Ma, W., and Huang, M. T. (1998). Inhibitory activity of boswellic acids from *Boswellia serrata* against human leukemia HL-60 cells in culture. *Planta Med.* 64, 328–331. doi: 10.1055/s-2006-957444
- Sharma, B., Salunke, R., Srivastava, S., Majumder, C., and Roy, P. (2009). Effects of guggulsterone isolated from *C. mukul* in high fat diet induced diabetic rats. *Food Chem. Toxicol.* 47, 2631–2639. doi: 10.1016/j.fct.2009.07.021
- Sharma, J. N., and Sharma, J. N. (1977). Comparison of the anti-inflammatory activity of *C. mukul* (an indigenous drug) with those of phenylbutazone and ibuprofen in experimental arthritis induced by mycobacterial adjuvant. *Arzneimittelforschung* 27, 1455–1457.

- Sharma, M. L., Bani, S., and Singh, G. B. (1989). Anti-arthritis activity of boswellic acids in bovine serum albumin (BSA)-induced arthritis. *Int. J. Immunopharmacol.* 11, 647–652. doi: 10.1016/0192-0561(89)90150-1
- Sheir, Z., Nasr, A. A., Massoud, A., Salama, O., Badra, G. A., El-Shennawy, H., et al. (2001). A safe, effective, herbal antischistosomal therapy derived from myrrh. *Am. J. Trop. Med. Hyg.* 65, 700–704. doi: 10.4269/ajtmh.2001.65.700
- Shelmadine, B. D., Bowden, R. G., Moreillon, J. J., Cooke, M. B., Yang, P., Deike, E., et al. (2017). A pilot study to examine the effects of an anti-inflammatory supplement on eicosanoid derivatives in patients with chronic kidney disease. *J. Altern. Complement. Med.* 23, 632–638. doi: 10.1089/acm.2016.0007
- Shen, Y., Takahashi, M., Byun, H. M., Link, A., Sharma, N., Balaguer, F., et al. (2012). Boswellic acid induces epigenetic alterations by modulating DNAmethylation in colorectal cancer cells. *Cancer Biol. Ther.* 13, 542–552. doi: 10.4161/cbt.19604
- Shi, J. J., Jia, X. L., Li, M., Yang, N., Li, Y. P., Zhang, X., et al. (2015). Guggulsterone induces apoptosis of human hepatocellular carcinoma cells through intrinsic mitochondrial pathway. *World J. Gastroenterol.* 21, 13277–13287. doi: 10.3748/wjg.v21.i47.13277
- Shishodia, S., and Aggarwal, B. B. (2004). Guggulsterone inhibits NF-kappaB and IkappaB kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. *J. Biol. Chem.* 279, 47148–47158. doi: 10.1074/jbc.M408093200
- Shishodia, S., Azu, N., Rosenzweig, J. A., and Jackson, D. A. (2015). Guggulsterone for chemoprevention of cancer. *Curr. Pharm. Des.* 22, 294–306. doi: 10.2174/1381612822666151112153117
- Shishodia, S., Harikumar, K. B., Dass, S., Ramawat, K. G., and Aggarwal, B. B. (2008). The guggul for chronic diseases: ancient medicine, modern targets. *Anticancer Res.* 28, 3647–3664.
- Shishodia, S., Sethi, G., Ahn, K. S., and Aggarwal, B. B. (2007). Guggulsterone inhibits tumor cell proliferation, induces S-phase arrest, and promotes apoptosis through activation of c-Jun N-terminal kinase, suppression of Akt pathway, and downregulation of antiapoptotic gene products. *Biochem. Pharmacol.* 74, 118–130. doi: 10.1016/j.bcp.2007.03.026
- Siddiqui, M. M., Afaq, S. H., and Asif, M. (1984). Chemical standardization of 'Kundur' (Oleo-Gum-Resin of *Boswellia serrata* Roxb). *Anc. Sci. Life.* 4, 48–50.
- Sinal, C. J., and Gonzalez, F. J. (2002). Guggulsterone: an old approach to a new problem. *Trends Endocrinol. Metab.* 13, 275–276. doi: 10.1016/S1043-2760(02)00640-9
- Singh, A. K., Prasad, G. C., and Tripathi, S. N. (1982). *In vitro* studies on thyrogenic effect of *C. mukul* (guggulu). *Anc. Sci. Life.* 2, 23–28.
- Singh, B. B., Mishra, L. C., Vinjamury, S. P., Aquilina, N., Singh, V. J., and Shepard, N. (2003). The effectiveness of *C. mukul* for osteoarthritis of the knee: an outcomes study. *Altern. Ther. Health Med.* 9, 74–79.
- Singh, R. B., Niaz, M. A., and Ghosh, S. (1994). Hypolipidemic and antioxidant effects of *Commiphora mukul* as an adjunct to dietary therapy in patients with hypercholesterolemia. *Cardiovasc. Drugs Ther.* 8, 659–664. doi: 10.1007/BF00877420
- Singh, R. P., Singh, R., Ram, P., and Batliwala, P. G. (1993). Use of Pushkar- Guggul, an indigenous antiischemic combination, in the management of ischemic heart disease. *Int. J. Pharmacol.* 31, 147–160. doi: 10.3109/13880209309082932
- Singh, S. K., Bhusari, S., Singh, R., Saxena, A., Mondhe, D., and Qazi, G. N. (2007). Effect of acetyl 11-keto beta-boswellic acid on metastatic growth factor responsible for angiogenesis. *Vascul. Pharmacol.* 46, 333–337. doi: 10.1016/j.vph.2006.09.008
- Singh, S. V., Choi, S., Zeng, Y., Hahm, E. R., and Xiao, D. (2007). Guggulsterone-induced apoptosis in human prostate cancer cells is caused by reactive oxygen intermediate dependent activation of c-Jun NH2-terminal kinase. *Cancer Res.* 67, 7439–7449. doi: 10.1158/0008-5472.CAN-07-0120
- Singh, S. V., Zeng, Y., Xiao, D., Vogel, V. G., Nelson, J. B., Dhir, R., et al. (2005). Caspase-dependent apoptosis induction by guggulsterone, a constituent of Ayurvedic medicinal plant *Commiphora mukul*, in PC-3 human prostate cancer cells is mediated by Bax and Bak. *Mol. Cancer Ther.* 4, 1747–1754. doi: 10.1158/1535-7163.MCT-05-0223
- Singh, S., Khajuria, A., Taneja, S. C., Khajuria, R. K., Singh, J., Johri, R. K., et al. (2008). The gastric ulcer protective effect of boswellic acids, a leukotriene inhibitor from *Boswellia serrata*, in rats. *Phytomedicine* 15, 408–415. doi: 10.1016/j.phymed.2008.02.017
- Singh, V., Kaul, S., Chander, R., and Kapoor, N. K. (1990). Stimulation of low density lipoprotein receptor activity in liver membrane of guggulsterone treated rats. *Pharmacol. Res.* 22, 37–44. doi: 10.1016/1043-6618(90)90741-U
- Song, J. J., Kwon, S. K., Cho, C. G., Park, S. W., and Chae, S. W. (2010). Guggulsterone suppresses LPS induced inflammation of human middle ear epithelial cells (HMEEC). *Int. J. Pediatr. Otorhinolaryngol.* 74, 1384–1387. doi: 10.1016/j.ijporl.2010.09.012
- Syrovetz, T., Buchele, B., Gedig, E., Slupsky, J. R., and Simmet, T. (2000). Acetyl-boswellic acids are novel catalytic inhibitors of human topoisomerases I and II alpha. *Mol. Pharmacol.* 58, 71–81. doi: 10.1124/mol.58.1.71
- Syrovetz, T., Büchele, B., Krauss, C., Laumonnier, Y., and Simmet, T. (2005a). Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-alpha induction in monocytes by direct interaction with I kappa B kinases. *J. Immunol.* 174, 498–506. doi: 10.4049/jimmunol.174.1.498
- Syrovetz, T., Gschwend, J. E., Büchele, B., Laumonnier, Y., Zugmaier, W., Genze, F., et al. (2005b). Inhibition of IkappaB kinase activity by acetyl-boswellic acids promotes apoptosis in androgen-independent PC-3 prostate cancer cells *in vitro* and *in vivo*. *J. Biol. Chem.* 280, 6170–6180. doi: 10.1074/jbc.M409477200
- Szapary, P. O., Wolfe, M. L., Bloedon, L. T., Cucchiara, A. J., DerMarderosian, A. H., Cirigliano, M. D., et al. (2003). Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. *JAMA* 290, 765–772. doi: 10.1001/jama.290.6.765
- Takada, Y., Ichikawa, H., Badmaev, V., and Aggarwal, B. B. (2006). Acetyl-11-keto-beta-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-kappa B and NF-kappa B-regulated gene expression. *J. Immunol.* 176, 3127–3140. doi: 10.4049/jimmunol.176.5.3127
- Takahashi, M., Sung, B., Shen, Y., Hur, K., Link, A., Boland, C. R., et al. (2012). Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. *Carcinogenesis* 33, 2441–2449. doi: 10.1093/carcin/bgs286
- Thappa, D. M., and Dogra, J. (1994). Nodulocystic acne: oral guggulipid versus tetracycline. *J. Dermatol.* 21, 729–731. doi: 10.1111/j.1346-8138.1994.tb03277.x
- Togni, S., Maramaldi, G., Bonetta, A., Giacomelli, L., and Di Pierro, F. (2015). Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. *Eur. Rev. Med. Pharmacol. Sci.* 19, 1338–1344.
- Togni, S., Maramaldi, G., Di Pierro, F., and Biondi, M. (2014). A cosmeceutical formulation based on boswellic acids for the treatment of erythematous eczema and psoriasis. *Clin. Cosmet. Investig. Dermatol.* 7, 321–327. doi: 10.2147/CCID.S69240
- Tripathi, S. N., Gupta, M., Sen, S. P., and Udupa, K. N. (1975). Effect of a keto-steroid of *Commiphora mukul* L. on hypercholesterolemia and hyperlipidemia induced by neomercazole and cholesterol mixture in chicks. *Indian J. Exp. Biol.* 13, 15–18.
- Tripathi, Y. B. (2009). BHUx: a patented polyherbal formulation to prevent hyperlipidemia and atherosclerosis. *Recent Pat. Inflamm. Allergy Drug Discov.* 3, 49–57. doi: 10.2174/187221309787158443
- Tripathi, Y. B., Malhotra, O. P., and Tripathi, S. N. (1984). Thyroid-stimulating action of Z-guggulsterone obtained from *C. mukul*. *Planta Med.* 50, 78–80. doi: 10.1055/s-2007-969626
- Urizar, N. L., Liverman, A. B., Dodds, D. T., Silva, F. V., Ordentlich, P., Yan, Y., et al. (2002). A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science* 296, 1703–1706. doi: 10.1126/science.1072891
- Verma, S. K., and Bordia, A. (1988). Effect of *Commiphora mukul* (gum guggulu) in patients of hyperlipidemia with special reference to HDL-cholesterol. *Indian J. Med. Res.* 87, 356–360.
- von Rhein, C., Weidner, T., Henß, L., Martin, J., Weber, C., Sliva, K., et al. (2016). Curcumin and *Boswellia serrata* gum resin extract inhibit chikungunya and vesicular stomatitis virus infections *in vitro*. *Antiviral Res.* 125, 51–57. doi: 10.1016/j.antiviral.2015.11.007
- Vyas, K. Y., Bedarkar, P., Galib, R., and Prajapati, P. K. (2015). Comparative Anti-hyperlipidaemic activity of Navina (fresh) and Purāṇa (old) Guggulu. *Anc. Sci. Life.* 35, 101–109. doi: 10.4103/0257-7941.171672
- Wang, Q., Pan, X., Wong, H. H., Wagner, C. A., Lahey, L. J., Robinson, W. H., et al. (2014). Oral and topical boswellic acid attenuates mouse osteoarthritis. *Osteoarthr. Cartil.* 22, 128–132. doi: 10.1016/j.joca.2013.10.012

- Wang, R., Wang, Y., Gao, Z., and Qu, X. (2014). The comparative study of acetyl-11-keto-beta-boswellic acid (AKBA) and aspirin in the prevention of intestinal adenomatous polyposis in APC(Min/+) mice. *Drug Discov. Ther.* 8, 25–32. doi: 10.5582/ddt.8.25
- Wang, W. C., Uen, Y. H., Chang, M. L., Cheah, K. P., Li, J. S., Yu, W. Y., et al. (2012). Protective effect of guggulsterone against cardiomyocyte injury induced by doxorubicin *in vitro*. *BMC Complement. Altern. Med.* 12:138. doi: 10.1186/1472-6882-12-138
- Wang, X., Greilberger, J., Ledinski, G., Kager, G., Paigen, B., and Jürgens, G. (2004). The hypolipidemic natural product *Commiphora mukul* and its component guggulsterone inhibit oxidative modification of LDL. *Atherosclerosis* 172, 239–246. doi: 10.1016/j.atherosclerosis.2003.10.008
- Wang, Y. G., Ma, Q. G., Tian, J., Ren, J., Wang, A. G., Ji, T. F., et al. (2016). Hepatoprotective triterpenes from the gum resin of *Boswellia carterii*. *Fitoterapia* 109, 266–273. doi: 10.1016/j.fitote.2015.12.018
- Wang, Y. G., Ren, J., Wang, A. G., Yang, J. B., Ji, T. F., Ma, Q. G., et al. (2013). Hepatoprotective prenylaromadendrane-type diterpenes from the gum resin of *Boswellia carterii*. *J. Nat. Prod.* 76, 2074–2079. doi: 10.1021/np400526b
- Weber, C. C., Reising, K., Müller, W. E., Schubert-Zsilavecz, M., and Abdel-Tawab, M. (2006). Modulation of Pgp function by boswellic acids. *Planta Med.* 72, 507–513. doi: 10.1055/s-2006-931536
- Wu, J., Xia, C., Meier, J., Li, S., Hu, X., and Lala, D. S. (2002). The hypolipidemic natural product guggulsterone acts as an antagonist of the bile acid receptor. *Mol. Endocrinol.* 16, 1590–1597. doi: 10.1210/mend.16.7.0894
- Xia, L., Chen, D., Han, R., Fang, Q., Waxman, S., and Jing, Y. (2005). Boswellic acid acetate induces apoptosis through caspase-mediated pathways in myeloid leukemia cells. *Mol. Cancer Ther.* 4, 381–388. doi: 10.1158/1535-7163.MCT-03-0266
- Xiao, D., and Singh, S. V. (2008). z-Guggulsterone, a constituent of Ayurvedic medicinal plant *C. mukul*, inhibits angiogenesis *in vitro* and *in vivo*. *Mol. Cancer Ther.* 7, 171–180. doi: 10.1158/1535-7163.MCT-07-0491
- Xiao, D., Zeng, Y., Prakash, L., Badmaev, V., Majeed, M., and Singh, S. V. (2011). Reactive oxygen species-dependent apoptosis by guggulipid extract of Ayurvedic medicine plant *Commiphora mukul* in human prostate cancer cells is regulated by c-Jun N-terminal kinase. *Mol. Pharmacol.* 79, 499–507. doi: 10.1124/mol.110.068551
- Xu, H. B., Fu, J., Huang, F., and Yu, J. (2017). Guggulsterone sensitized drug-resistant human hepatocarcinoma cells to doxorubicin through a Cox-2/P-gp dependent pathway. *Eur. J. Pharmacol.* 803, 57–64. doi: 10.1016/j.ejphar.2017.03.045
- Xu, H. B., Li, L., and Liu, G. Q. (2011). Reversal of multidrug resistance by guggulsterone in drug-resistant MCF-7 cell lines. *Chemotherapy* 57, 62–70. doi: 10.1159/000321484
- Xu, H. B., Shen, Z. L., Fu, J., and Xu, L. Z. (2014a). Reversal of doxorubicin resistance by guggulsterone of *Commiphora mukul* *in vivo*. *Phytomedicine* 21, 1221–1229. doi: 10.1016/j.phymed.2014.06.003
- Xu, H. B., Xu, L. Z., Li, L., Fu, J., and Mao, X. P. (2012). Reversion of P-glycoprotein-mediated multidrug resistance by guggulsterone in multidrug-resistant human cancer cell lines. *Eur. J. Pharmacol.* 694, 39–44. doi: 10.1016/j.ejphar.2012.06.046
- Xu, H. B., Xu, L. Z., Mao, X. P., and Fu, J. (2014b). Guggulsterone of *Commiphora mukul* resin reverses drug resistance in imatinib-resistant leukemic cells by inhibiting cyclooxygenase-2 and P-glycoprotein. *Phytomedicine* 21, 1004–1009. doi: 10.1016/j.phymed.2014.02.014
- Xu, Y., Watanabe, T., Tanigawa, T., Machida, H., Okazaki, H., Yamagami, H., et al. (2010). Bile acids induce *cdx2* expression through the farnesoid x receptor in gastric epithelial cells. *J. Clin. Biochem. Nutr.* 46, 81–86. doi: 10.3164/jcbn.09-71
- Y, J., Kamath, J. V., and Asad, M. (2006). Effect of hexane extract of *B. serrata* oleo-gum resin on chemically induced liver damage. *Pak. J. Pharm. Sci.* 19, 129–133.
- Yadav, V. R., Prasad, S., Sung, B., Gelovani, J. G., Guha, S., Krishnan, S., et al. (2012). Boswellic acid inhibits growth and metastasis of human colorectal cancer in orthotopic mouse model by downregulating inflammatory, proliferative, invasive and angiogenic biomarkers. *Int. J. Cancer* 130, 2176–2184. doi: 10.1002/ijc.26251
- Yamada, T., and Sugimoto, K. (2016). Guggulsterone and its role in chronic diseases. *Adv. Exp. Med. Biol.* 929, 329–361. doi: 10.1007/978-3-319-41342-6_15
- Yamada, T., Osawa, S., Ikuma, M., Kajimura, M., Sugimoto, M., Furuta, T., et al. (2014). Guggulsterone, a plant-derived inhibitor of NF- κ B, suppresses CDX2 and COX-2 expression and reduces the viability of esophageal adenocarcinoma cells. *Digestion* 90, 208–217. doi: 10.1159/000365750
- Yang, J. Y., Della-Fera, M. A., and Baile, C. A. (2008). Guggulsterone inhibits adipocyte differentiation and induces apoptosis in 3T3-L1 cells. *Obesity* 16, 16–22. doi: 10.1038/oby.2007.24
- Yang, J. Y., Della-Fera, M. A., Rayalam, S., Ambati, S., and Baile, C. A. (2007). Enhanced pro-apoptotic and anti-adipogenic effects of genistein plus guggulsterone in 3T3-L1 adipocytes. *Biofactors* 30, 159–169. doi: 10.1002/biof.5520300303
- Yang, L., Broderick, D., Jiang, Y., Hsu, V., and Maier, C. S. (2014). Conformational dynamics of human FXR-LBD ligand interactions studied by hydrogen/deuterium exchange mass spectrometry: insights into the antagonism of the hypolipidemic agent Z-guggulsterone. *Biochim. Biophys. Acta* 1844, 1684–1693. doi: 10.1016/j.bbapap.2014.06.007
- Yang, M. H., Lee, K. T., Yang, S., Lee, J. K., Lee, K. H., Moon, I. H., et al. (2012). Guggulsterone enhances antitumor activity of gemcitabine in gallbladder cancer cells through suppression of NF- κ B. *J. Cancer Res. Clin. Oncol.* 138, 1743–1751. doi: 10.1007/s00432-012-1254-7
- Youn, H. S., Ahn, S. I., and Lee, B. Y. (2009). Guggulsterone suppresses the activation of transcription factor IRF3 induced by TLR3 or TLR4 agonists. *Int. Immunopharmacol.* 9, 108–112. doi: 10.1016/j.intimp.2008.10.012
- Yuan, H. Q., Kong, F., Wang, X. L., Young, C. Y., Hu, X. Y., and Lou, H. X. (2008). Inhibitory effect of acetyl-11-keto-beta-boswellic acid on androgen receptor by interference of Sp1 binding activity in prostate cancer cells. *Biochem. Pharmacol.* 75, 2112–2121. doi: 10.1016/j.bcp.2008.03.005
- Zhang, J. H., Shangguan, Z. S., Chen, C., Zhang, H. J., and Lin, Y. (2016). Anti-inflammatory effects of guggulsterone on murine macrophage by inhibiting LPS-induced inflammatory cytokines in NF- κ B signaling pathway. *Drug Des. Devel. Ther.* 10, 1829–1835. doi: 10.2147/DDDT.S104602
- Zhao, W., Entschladen, F., Liu, H., Niggemann, B., Fang, Q., Zaenker, K. S., et al. (2003). Boswellic acid acetate induces differentiation and apoptosis in highly metastatic melanoma and fibrosarcoma cells. *Cancer Detect. Prev.* 27, 67–75. doi: 10.1016/S0361-090X(02)00170-8
- Zhong, F., Tong, Z. T., Fan, L. L., Zha, L. X., Wang, F., Yao, M. Q., et al. (2016). Guggulsterone-induced apoptosis in cholangiocarcinoma cells through ROS/JNK signaling pathway. *Am. J. Cancer Res.* 6, 226–237.
- Zhong, F., Yang, J., Tong, Z. T., Chen, L. L., Fan, L. L., Wang, F., et al. (2015). Guggulsterone inhibits human cholangiocarcinoma Sk-ChA-1 and Mz-ChA-1 cell growth by inducing caspase-dependent apoptosis and downregulation of survivin and Bcl-2 expression. *Oncol. Lett.* 10, 1416–1422. doi: 10.3892/ol.2015.3391
- Zhou, X., Cai, J. G., Zhu, W. W., Zhao, H. Y., Wang, K., and Zhang, X. F. (2015). Boswellic acid attenuates asthma phenotype by downregulation of GATA3 via inhibition of pSTAT6. *Genet. Mol. Res.* 14, 7463–7468. doi: 10.4238/2015.July.3.22
- Zhu, N., Rafi, M. M., DiPaola, R. S., Xin, J., Chin, C. K., Badmaev, V., et al. (2001). Bioactive constituents from gum guggul (*Commiphora wightii*). *Phytochemistry* 56, 723–727. doi: 10.1016/S0031-9422(00)00485-4

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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