Review

The genus Commiphora: A review of its traditional uses, phytochemistry and pharmacology

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A B S T R A C T

Ethnopharmacological relevance: The resinous exudates of the Commiphora species, known as ‘myrrh’, are used in traditional Chinese medicine for the treatment of trauma, arthritis, fractures and diseases caused by blood stagnation. Myrrh has also been used in the Ayurvedic medical system because of its therapeutic effects against inflammatory diseases, coronary artery diseases, gynecological disease, obesity, etc.

Aim of the review: Based on a comprehensive review of traditional uses, phytochemistry, pharmacological and toxicological data on the genus Commiphora, opportunities for the future research and development as well as the genus’ therapeutic potential are analyzed.

Methods: Information on the Commiphora species was collected via electronic search (using Pubmed, SciFinder, Scirus, Google Scholar and Web of Science) and a library search for articles published in peer-reviewed journals. Furthermore, information also was obtained from some local books on ethnopharmacology. This paper covers the literature, primarily pharmacological, from 2000 to the end of December 2011.

Results: The resinous exudates from the bark of plants of the genus Commiphora are important indigenous medicines, and have a long medicinal application for arthritis, hyperlipidemia, pain, wounds, fractures, blood stagnation, in Ayurvedic medicine, traditional Chinese medicine and other indigenous medical systems. Phytochemical investigation of this genus has resulted in identification of more than 300 secondary metabolites. The isolated metabolites and crude extract have exhibited a wide of in vitro and in vivo pharmacological effects, including antiproliferative, antioxidant, anti-inflammatory and antimicrobial. The bioactive steroids guggulsterones have attracted most attention for their potent hypolipidemic effect targeting farnesoid X receptor, as well as their potent inhibitory effects on tumor cells and anti-inflammatory efficiency.

Conclusions: The resins of Commiphora species have emerged as a good source of the traditional medicines for the treatment of inflammation, arthritis, obesity, microbial infection, wound, pain, fractures, tumor and gastrointestinal diseases. The resin of C. mukul in India and that of C. molmol in Egypt have been developed as anti-hyperlipidemia and antischistosomal agents. Pharmacological results have validated the use of this genus in the traditional medicines. Some bioassays are difficult to reproduce because the plant materials used have not been well identified, therefore analytical protocol and standardization of extracts should be established prior to biological evaluation. Stem, bark and leaf of this genus should receive more attention. Expansion of research materials would provide more opportunities for the discovery of new bioactive principles from the genus Commiphora.

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Abbreviations: ABTS, 2,2’-azino-di-[3-ethylbenzthiazoline sulphonate]; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COX, cyclooxygenase; CNS, central nervous system; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FXR, farnesoid X receptor; GC, gas chromatography; HDL, high density lipoprotein; HUVEC, human umbilical vein endothelial cells; IL, interleukin; INOS, inducible nitric oxide synthase; JNK, c-Jun NH2-terminal kinase; LDH, lactate dehydrogenase; LDL, low density lipoprotein; 5-LOX, 5-lipoxygenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIC, minimum inhibitory concentration; NO, nitric oxide; ODC, ornithine decarboxylase; PLA2, phospholipase A2; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; SOD, superoxide dismutase; TG, triglyceride; TID, times a day; TNF, tumor necrosis factor; TPA, 12-O-tetradecanoylphorbol-13-acetate; VAS, visual analogue scale; VEGF, vascular endothelial growth factor; VLDL, very-low-density lipoprotein

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1. Introduction

The plant resinous exudates, exemplified by frankincense, myrrh, benzoin, Dragón's blood and feralae resina, are important resources for traditional medicines. Their medicinal functions and usages are recorded in the ancient literature of Egypt, Rome, Greece, and China (Langenheim, 2003; Nanjing University of Chinese Medicine, 2006). Myrrh, originating from Arabia, is the exudates produced by the secretory tissue in the bark of Commiphora species.

The genus Commiphora (Bursereaceae) with more than 150 plant species, is distributed in the tropical and subtropical regions, especially occurring in northeastern Africa, southern Arabia and India (Langenheim, 2003; Vollesen, 1989). The plants of Commiphora species are characterized as small trees or shrubs with spinescent branches, pale-gray bark and reddish-brown resinous exudates.

The resinous exudates of the genus Commiphora are commonly used as perfume, incense, or embalming ointment, and their medicinal values have been gradually recognized by humankind (Langenheim, 2003). They are used in indigenous medicines for the treatment of wound, pain, arthritis, fractures, obesity, parasitic infection and gastrointestinal diseases (Al-Harbi et al., 1997; Zhang, 2009; Abdul-Ghani et al., 2009). Diverse secondary metabolites including terpenoids, steroids, flavonoids, sugars, lignans, etc. have been discovered in this genus (Hanuš et al., 2005). Antiproliferative, anti-inflammatory, antimicrobial, hepatoprotective and cardiovascular properties of the purified metabolites and the crude extracts have been investigated (El Ashry et al., 2003; Shen and Lou, 2008; Deng, 2007).

The distribution of fifty-one constituents and medical uses of myrrh was reviewed by El Ashry et al. (2003). A review covering the chemical aspects of Commiphora species has appeared (Hanuš et al., 2005). Two reviews dealing with the hypolipidemic property of guggul (the resin of Commiphora mukul) has been published (Ulbricht et al., 2005; Sahni et al., 2005). The resin of C. molmol mainly used in Egypt as an antiparasitic agent, its medical use has been summarized recently (Abdul-Ghani et al., 2009; Tonkal and Morsy, 2008). The hypolipidemic property of guggulsterones (Ramawat and Merillon, 2008) and their molecular targets (Shishodia et al., 2008), the bioactive compounds from the genus Commiphora and Boswellia have been reviewed (Shen and Lou, 2008). Plant resins with antimicrobial potential have been summarized, the resin of Commiphora species were included (Termentzi et al., 2011). Different from the writing objectives of above literatures, our review presents a comprehensive and up-to-date report on traditional uses, phytochemical aspects, pharmacological functions and toxicity of this genus. Besides, we focus on the pharmacological data reported since the year of 2000, to provide a probable scope of future research concerning this genus.

2. Traditional uses

Traditional uses, local names and the main pharmacological activities of some Commiphora species from different regions are listed in Table 1. The most frequently employed and investigated Commiphora species are Commiphora myrrha, C. opobalsamum, C. mukul and C. molmol. The resins of these Commiphora species exhibit diverse therapeutic utilities, such as wound, pain, fracture, mouth ulcer, inflammatory disease, stomach disorders and microbial infection.

The recognition of the therapeutic and medicinal value of myrrh (known as guggul in India, the resinous exudates of C. mukul) in Ayurvedic medical system dates from 3000 years ago. Guggul is regarded as the most important herb in the authoritative monograph Charaka Samhita for the treatment of obesity, and is used as a hypolipidemic agent to treat lipid disorder (Kuppurajan et al., 1978; Singh et al., 1994; Khanna et al., 2010). This resin is used for promoting the bone fractures union, sore throat, mouth ulcer, wounds, skin disorders, acne, intestinal worms, lymphadenopathy, as recorded in Bhava Prakash's...
<table>
<thead>
<tr>
<th>Species</th>
<th>Regions</th>
<th>Local name</th>
<th>Traditional use</th>
<th>Pharmacological activity</th>
<th>Extract/constituents evaluated</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Greece</td>
<td></td>
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<td>Wounds, worms, sepisis, cough, snakebite, infections in mouth, teeth, and eyes</td>
<td>Antimicrobial</td>
<td>Resin</td>
<td>Omer and Auffray (2005)</td>
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<td>Britain</td>
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<td></td>
<td>Pharyngitis, tonsillitis, gingivitis, ulcers, cough, proctitis, sinusitis and skin inflammation</td>
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<td>Bradley (1992)</td>
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<td>France</td>
<td></td>
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<td>Nasal congestion caused by common cold, small wounds, and infection of the buccal cavity</td>
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<td>Bruneton (1995)</td>
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<td>Germany America</td>
<td>Myrrh</td>
<td></td>
<td>Oral diseases Sore throats, oral mucosal and gingival irritations</td>
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<td>Resin tincture</td>
<td>Schilcher (1997)</td>
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<tr>
<td><em>Commiphora mukul</em> (Hook. ex Stocks) Engl.</td>
<td>India</td>
<td>Guggul, gugulu</td>
<td>Bone fracture, wound, skin disorders, inflammatory disease, arthritis, mouth ulcer, cardiovascular disease, lipid disorder, obesity, and hypothyroidism</td>
<td>Anti-inflammatory</td>
<td>Ethyl acetate extract Triterpenoids diterpenoids, steroids</td>
<td>Sharma et al. (2009); Saxena et al. (2007) Sharma et al. (2005); Singh et al. (2005); Xiao and Singh (2008); Mada et al. (2011) Annu et al. (2010); Vikneswaran et al. (2008)</td>
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<td><em>Commiphora caudata</em> Engl.</td>
<td>India</td>
<td>Kilimaram, Idingil, Kizhuvam, Mankiluvai Mankiluvai</td>
<td>Inflammation, pain, and relieving stomach aches</td>
<td>Analgesic Anti-inflammatory</td>
<td>Ethanol extract of leaves; Endosperm of the seeds</td>
<td>Gowri Shankar et al. (2008); Gowrishankar et al. (2004)</td>
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<td><em>Commiphora berryi</em> Engl.</td>
<td>India</td>
<td>Mukiulvai</td>
<td>Cold, fever, and wound</td>
<td>Gastric antulcer Hepatoprotective Antioxidant</td>
<td>Methanol extract</td>
<td>Gowri Shankar et al. (2008); Gowrishankar et al. (2004)</td>
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<tr>
<td><em>Commiphora holtziana</em> Engl.</td>
<td>Eastern Africa</td>
<td>Gum hagger</td>
<td>Kill and repel tick pest populations on camel and cattle</td>
<td>Analgesic Antiectoparasitic</td>
<td>Aqueous suspension Terpenoids</td>
<td>Kokwaro (1976)</td>
</tr>
</tbody>
</table>

Table 1
Medicinal uses of selected *Commiphora* species.
### 3. Phytochemical studies

More than 300 molecules have been identified from this genus. The information of isolated metabolites has been provided by El Ashry et al. (2003) and Hanuš et al. (2005), introduced from the points of plant origin and species. In present review important phytochemical regularities and findings since 2005 of this genus are introduced. A comprehensive summary of structures and resources of metabolites classified by structural types was given in Supplementary Data.

With respect to phytochemical aspects of this genus, the characteristics as follows deserve our full attention. (i) Terpenoids especially the sesqui- and triterpenoids are the most abundant constituents in this genus. (ii) The species of \( C. myrrha \), \( C. mukul \), \( C. kua \) and \( C. confusa \) have received more phytochemical attention. (iii) The resinous exudates of \( C. myrrha \) species are dispensed on prescription in the indigenous medicines of China, India, Egypt, etc. Therefore, the resins but not the leaves, barks and stems of this genus, are the most commonly investigated targets for discovering bioactive compounds.

#### 3.1. Terpenoids

##### 3.1.1. Monoterpenoids, sesquiterpenoids and volatile oil

Monoterpenoids mainly occur in volatile oil, and identified by gas chromatography (GC)-based techniques. Many papers have described the GC analysis of volatile oil from different \( C. myrrha \) species, covering \( C. myrrha \) (Dekebo et al., 2002a; Mortezasemmeni and Saeedi, 2003), \( C. guidottii \) (Craveiro et al., 1983), \( C. quadricincta \) (Assad et al., 1997), \( C. opobalsamum \) (Dekebo et al., 2002a; Morteza-Semnani and Saeedi, 2003), \( C. molmol \) (Provan et al., 1998), \( C. holtziana \) (Provan et al., 1998) and \( C. sphaerocarpa \) and \( C. katad \) (Dekebo et al., 2002a). Monoterpenoids including \( \alpha \)-pinene, camphene, \( \beta \)-pinene, myrcene and limonene have been detected. It was observed that the composition of volatile oil from different \( C. myrrha \) species varies largely. Sesquiterpenoids with low degree of oxidation play a dominant role in volatile oil. \( \beta \)-Elemene, \( \alpha \)-copaene, \( \alpha \)-humulene, \( \beta \)-selinene and germacrene B are widely distributed sesquiterpenoids in the volatile oil of different \( C. myrrha \) species.

Fig. 1 The structures of sesquiterpenoids from the genus \( C. myrrha \) are mainly classified into germacrane, eudesmane, guaiane, cadinane, elemane, bisabolane and oplopane groups. The presence of furanosesquiterpenoids is characteristics of this genus.

### Table 1 (continued)

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<thead>
<tr>
<th>Species</th>
<th>Local name</th>
<th>Traditional use</th>
<th>Pharmacological activity</th>
<th>Extracts/constituents evaluated</th>
<th>Phytochemical aspects</th>
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<td>Commiphora kua Vollesen</td>
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<td>Commiphora erlangnum Eng.</td>
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<td>Commiphora harveyi (Engl.)</td>
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<td>Commiphora mecherki Eng.</td>
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<td>Commiphora guidottii Chiu.</td>
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<td>Commiphora kabynskyi (O. Reh.</td>
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<td>Commiphora koynskyi Eng.</td>
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<td>Commiphora myrrha (Threth.)</td>
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<td>Commiphora myrrha (Threth.)</td>
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<td>Commiphora kua Vollesen</td>
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Materia Medica (Murthy, 1998). It is also used for the treatment of inflammatory diseases, arthritis and pain in India (Ding and Staudinger, 2005; Singh et al., 2003). The resin of \( C. molmol \) is now sold as an antiparasitic agent sold in the market with a commercial name of Mirazid in Egypt (Abdul-Ghani et al., 2009).

Myrrh is used in the Arab medicine for the treatment of inflammation-related diseases and stomach diseases (Al-Harbi et al., 1997).

Myrrh in China is used since the Tang Dynasty in 600 AD, and this has been recorded in the Chinese medical document \( Hai Yao Ben Cao \). Myrrh used in China is the resin of \( C. myrrha \) or \( C. opobalsamum \). It is prescribed together with frankincense for the treatment of pain, swelling, trauma, arthritis and fractures (Zhang, 2009). It is widely used in dermatology to treat skin ulcer, erythrosis and sore (Dai et al., 2001; Shang and Lu, 2007).

Medicinal applications of myrrh for trauma, arthritis, fractures and tumors originate from its abilities of breaking up congealed blood and promoting the blood circulation (Yifang, 2002; State Administration of Traditional Chinese Medicine, 1996). China has turned into the largest myrrh-importing country of the world, most of which is for medicinal consumption (Coppen, 1995).
More than twenty furanosesquiterpenoids covering furanogerma-
crane, furanoeudesmanes, furanoguaiane, furanocadinane and fur-
anoelemene have been discovered (Table S1 and Fig. S1), since the
first isolation of furanosesquiterpenoid from C. molmol (Brieskorn
and Noble, 1980). The discovery of sesquiterpenoid lactones,
identified to be germacrone (1), eudesmanolides (2 and 3),

Fig. 1. Chemical structures of typical constituents isolated from Commiphora species.
3.2. Steroids

Steroids are only found in the species of *C. mukul* in 1950 (Bhati, 1950). Cembrane diterpenoids and verticillane diterpenoids are also present in the same species (Table S2). Recently, a pimarane diterpenoid sandaracopimaric acid (8) and two abietane diterpenoids abietic acid (9) and dehydroabietic acid (10) have been reported from *C. myrrha* (Su et al., 2009).

3.3. Miscellaneous

In *Commiphora* species, many other secondary metabolites are encountered such as carbohydrates, flavonoids, lignans and long chain aliphatic derivatives (Table S5 and Fig. S5). Carbohydrates have been reported from the gum of *Commiphora*, and commonly exist in the form of polysaccharide (Hough et al., 1952; Jones and Nunn, 1955; Bose and Gupta, 1964). Acid hydrolysis of the gum produces mono- or di-saccharides. The flavonoids of this genus are found in the flower, stem and bark, but not obtained in the resinous exudates. 1,2,3,4-tetrahydroxy long chain aliphatic derivatives occur in the gum, for instance, D-xylo-guggultetrol-18 and guggultetrol-20 (Patil et al., 1973), which commonly exist in the form of furelllic acid ester or glycoside (Zhu et al., 2001; Shen et al., 2007).

3.4. Pharmacological and toxicological aspects

4.1. Anti-inflammatory activity

The resin of *C. mukul*, known as ‘guggul’ in Ayurvedic medicine, has been used for the therapy of arthritis for centuries. A clinical study indicated that the resin extract of *C. mukul* had significant improvements of osteoarthritis when treated with a dose of 500 mg TID for 1 month (Singh et al., 2003).

The MeOH resin extract of *C. mukul* demonstrated significant inhibition of NO formation in lipopolysaccharide (LPS)-activated murine macrophages with an IC$_{50}$ value of about 15 µg/mL (Meselhy, 2003; Matsuda et al., 2004a). Anti-inflammatory mechanism of MeOH extract against LPS-induced inflammation has been reported recently (Cheng et al., 2011). Cembrane diterpenoids, polypodane triterpenoids, steroids and lignans isolated from this species have been tested for their NO production and COX inhibitory activities. Z- and E-guggulsterones (21 and 22), myrrhanol A (23) and myrrhanone A (24) prevented NO production with IC$_{50}$ values of 1.1, 3.3, 21.1 and 42.3 µM, respectively (Meselhy, 2003). Myrrhanol A (23) and mukulol (25) inhibited the induction of inducible nitric oxide synthase (iNOS) in LPS-activated mouse peritoneal macrophages (Matsuda et al., 2004a). Concerning the COX inhibitory effect, cembrene (26) and E-guggulsterone (22) are most active, with 79% and 67% inhibition against COX-1, and with 83% and 54% inhibition against COX-2 at 100 ppm (Francis et al., 2004).

Z- and E-guggulsterones (21 and 22) have been found to exert their anti-inflammatory properties by suppressing activation of NF-κB and expression of NF-κB-regulated gene products (Shishodia and Aggarwal, 2004; Lv et al., 2008). An in vivo study accounts for anti-uveitis property of 21 and 22 has been carried out using Lewis rats. The results showed that 21 and 22 decreased the level of inflammatory markers, such as MMP-2, NO and PGE2, and prevented the expression of inflammation related protein in eye tissues (Kaliraiya et al., 2010).

Kimura et al. (2001) have studied anti-inflammatory activity of 23, 24 and the resin extract of *C. mukul* using adjuvant-induced air pouch granuloma model. 23 exhibited 7.9, 5.0 and 3.6 times more potent activities on carrmine content, granuloma weight and pouch fluid weight than the control drug hydrocortisone, and it has a potential to be developed as an anti-inflammatory agent. The EtOAc resin extract of *C. mukul* significantly prevented the LPS-induced nitrite release, ROS generation, and down-regulated the expression of COX-2, glial fibrillary protein and TNF-α in rat astrocytoma cells, suggesting its potential use on neuron-inflammation associated conditions in CNS disorders (Niranjan et al., 2010). The resin extract of *C. mukul* and guggulsterol exhibited inhibitory effect of MAPK, and down regulation of some inflammatory mediators such as TNF-α, II-1β and II-2 in peripheral blood mononuclear cells. It prompted that *C. mukul* and its metabolites might exert their anti-inflammatory property by inhibiting MAPK which regulates a variety of inflammation related genes (Manjula et al., 2006).

The extracts of *C. molmol* and *C. pyracanthoides* have been evaluated for their anti-inflammatory properties. The volatile oil of *C. molmol* was shown to inhibit the production of IL-1β-stimulated IL-6 and IL-8 in human gingival fibroblasts cells (Tipton et al., 2003). The petroleum ether extract of *C. molmol* resin showed inhibitory activity against carrageenan induced inflammation and cotton pellet granuloma (Tariq et al., 1985). Ten *Commiphora* species were evaluated for their anti-inflammatory activity using a 5-lipoxygenase (5-LOX) assay, and the stem extract of *C. pyracanthoides* was most active with IC$_{50}$ of 27.86 µg/ml (Paraskeva et al., 2008). The petroleum ether bark extract of *C. berryi* and the purified friedelin showed soybean lipoxygenase inhibitory effects with IC$_{50}$ values of 15.3 µg/mL and 35.8 µM (Kumari et al., 2011b).

The hexane extract of *C. erythraea* resin inhibited edematous response with 84% reduction at a dose of 1000 µg/cm$^2$ in croton oil-induced mice ear edema assay. Myrrhonone (27), rel-3R-methoxy-4S-furanogermacre-1E,10(15)-dien-6-one (28) and rel-2R-methoxy-4R-furanogermacr-1(10)E-en-6-one (29) isolated from this extract might be responsible for the antiedematous effect (Fraternale et al., 2011). Oral administration of the ethanol leaf
extracts of *C. caudata* at a dose of 250 mg/kg, inhibited 67% the carrageenan-induced paw oedema response in rat (Annun et al., 2010). The anti-inflammatory effects of mansumbinoic acid (30) and 2α,3β,23-trihydroxyolean-12-ene (31) have been verified in vivo (Duwiejua et al., 1993; Fourie and Snyckers, 1989).

As summarized above, the resin of *C. mukul* is most frequently investigated, and displays evident anti-inflammatory properties in *vitro* and in *vivo*, which validates its traditional use in Ayurvedic medicine. Steroids (especially 21 and 22) and triterpenoids (23 and 24) are the anti-inflammatory substances of *C. mukul*. The mechanism of action related to multiple inflammation-related proteins and signal pathways have been discussed, and COX, NO formation, ROS, TNF-α, PGE2, NF-κB and MAPK have been verified as potential anti-inflammatory targets.

### 4.2. Analgesic activity

The 85% EtOH extract (EE) and petroleum ether fraction (PEE) of *C. myrrha* displayed significant inhibitory effect of acetic acid-induced writhes, while not active in the hot plate assay. This result suggested that the analgesic activity of above samples might be mediated via peripheral pathways, but not a central one. Ethyl acetate fraction together with EE and PEE exerted analgesic effects though decreasing PGE2 level in formalin induced pain model (Su et al., 2011). Rats pretreated with 10% suspension of *C. molmol* resin, curzarenne (32) or furanouedensna-1,3-diene (33) increased the licking latency in a hot plate test. 33 reduced the number of writhes caused by intraperitoneal administration of acetic acid. The analgesic effects of 32 and 33 were reversed by naloxone, indicating this analgesic activity was exerted by an interaction with brain opioid mechanism (Dolara et al., 1996). The ethanol leaf extract of *C. caudata* inhibited 73.44% writhing response at a dose of 250 mg/kg in acetic acid induced mice writhing model (Annun et al, 2010). The analgesic activity of Commiphora extract and pure compounds supported the use of myrrh for wound, pain and bone fracture in indigenous medicines.

### 4.3. Inhibition of tumor-cell proliferation in vitro and in vivo

The crude extracts of different *Commiphora* species, dealing with *C. myrrha*, *C. molmol*, and *C. mukul*, have been investigated for their antiproliferative properties against tumor cells. Shoemaker et al. (2005) reported the inhibitory effects of the aqueous extract of *C. myrrha* resin against eight tumor cell lines. The volatile oil of *C. molmol* decreased the cell viability of human gingival fibroblasts and epithelial cells at concentrations of above 0.0025% and 0.0011% (Tipton et al., 2003). The resin of *C. molmol* exhibited antitumor activity in Ehrlich-solid-tumor-bearing mice in vivo. With treatment at dose of 250 and 500 mg/kg/d, its antitumor property was comparable to the standard drug cyclophosphamide (Al-Harbi et al., 1994). The MeOH extract of *C. mukul* resin prevented benzoyl peroxide and ultraviolet light-induced skin tumor promotion in Swiss mice (Sharma et al., 2005). Ten *Commiphora* species collected in South Africa were evaluated for antiproliferative activities against human colonic adenocarcinoma HT-29, human breast adenocarcinoma MCF-7 and human glioblastoma SF-268 cell lines. The plant materials were extracted by CH3OH-CHCl3 (1:1). The leaf and stem extracts of *C. glandulosa* were most active against HT-29 cell with IC50 values of about 50 μg/mL. While the leaf extract of *C. africana* exhibited highest inhibitory effect against MCF-7, with an inhibitory rate of 53% at 100 μg/mL (Paraskeva et al., 2008).

Guggulsterones (21 and 22) inhibited the proliferation of a wide variety of human tumor cell lines, including leukemia, multiple myeloma, head and neck carcinoma, lung carcinoma, melanoma, breast carcinoma, ovarian carcinoma and kidney cancer. They were also active against gleevec-resistant leukemia, dexamethasone-resistant multiple myeloma and doxorubicin-resistant breast cancer cells (Shishodia et al., 2007). The suppression of cell proliferation was completed by the inhibition of DNA synthesis and cell cycle arrest in S-phase. The induced apoptosis property of 21 and 22 has been detected through the activation of JNK, suppression of Akt and down-regulation of anti-apoptotic protein expression. 21 was able to inhibit the growth PC-3 and LNCaP cells by inducing apoptosis (Singh et al., 2005, 2007). Further study showed that its anti-prostate property was mediated by Bax and Bak, reactive oxygen intermediate-dependent activation of JNK, and inhibition of androgen receptor-promoter activity. Later, it was reported that 21 was an inhibitor of angiogenesis. It showed inhibition on the capillary-like tube formation in HUVEC cells, and migration in HUVEC and DU145 cells by suppressing the secretion of proangiogenic growth factors. This effect was confirmed by decrease in tumor burden, microvessel area and VEGF-R2 protein expression in male nude mice (Xiao and Singh, 2008). Pretreatment of 21 at a dose of 1.6 μM per mouse significantly inhibited the skin edema and hyperplasia in TPA-induced mouse skin tumorigenesis model. 21 also reduced tumor incidence, lowered tumor body burden, and delayed tumor appearance in SENCAR mouse skin tumorigenesis model (Sarfaraz et al., 2008). In addition, 21 prevented the smokeless tobacco and nicotine-induced head and neck squamous cell carcinoma by inhibiting the activation of NF-κB pathway and STAT3 pathway (Macha et al., 2011; Leeman-Neill et al., 2009). As an inhibitor of NF-κB activation, it could suppress RANKL and tumor cell-induced osteoclastogenesis, which was correlated with NF-κB activation (Ichikawa and Aggarwal, 2006).

The cytotoxicities of erlengarins A–D were tested against two human cells Hela and EAcy926, and two murine cells L929 and RAW 264.7. Erlingerins C and D demonstrated potent cytotoxicities, even comparable with the control podophyllotoxin (Hattemarium, 2003). Picropolygamin and lupeol exhibited cytotoxicities against human fibrosarcoma HT1080 cells with EC50 values of 1.9 and 16.7 μg/mL (Nakanishi et al., 2005).

A series of cycloartane-type triterpenoids (11–19) were isolated from *C. opobalsamum* and evaluated for their anti-prostate tumor activity against PC3 and DU145 cells (Shen et al., 2007, 2008b). Cycloarten-24-ene-1α,2α,3β-triol (11) was an inhibitor of the production of androgen receptor (AR) in LNCaP cells. Octadecane-1,25,35,4R-tetrol 1–O–2α,1–rhamnopyranoside showed inhibitory effect against PC3 and LNCaP cells, with IC50 values of 22.1 and 23.6 μM (Shen et al., 2007). In addition, 2-methoxy-5-acetoxy-furanogermacr-1(10)-en-6-one (34) and 29 exhibited inhibitory effect against LNCaP cells by suppressing AR nuclear translocation and/or interrupting the interaction between AR and the coactivators ARA70 and SRC-1 (Wang et al., 2011).

The mixture of two ferrulic acid derivatives (35 and 36) exhibited antiproliferative effect against human prostate cancer PC3 and breast cancer MCF-7 cells. It inhibited the proliferation of P388/MDR cells, suggesting that it might be able to overcome the P-glycoprotein-mediated drug resistance (Zhu et al., 2001). Dehydroabietic acid (10) and 34 possessed potent aromatase inhibitory activity with IC50 values of 0.32 and 0.21 μM, while sandaracopimaric acid (8) has 44% inhibition against aromatase at 0.30 μM, suggesting that these compounds have the potential for the treatment of breast cancer. In addition, sandaracopimaric acid (8), abietic acid (9) and dehydroabietic acid (10) inhibited the proliferation of human umbilical vein endothelial cells, with IC50 values of 0.122, 0.125 and 0.069 μM (Su et al., 2009).

### 4.4. Antiparasitic and antimicrobial activities

Mirazid, a drug containing 300 mg purified resin extract of *C. molmol*, is sold in the market as an antiparasitic drug. The resin
extract of *C. molmol* as schistosomicide, fasciolicide, heterophy- cide, dirocoeliasis and mollusidide have been reviewed in detail and provided sufficient evidence for its uses as antiparasitic agent (Abdul-Ghani et al., 2009). Subsequently, it was found that the resin of *C. molmol* and Mirazid displayed therapeutic effect on hepatic coccidiosis induced by the parasite *Eimeria stiedae* in domestic rabbits (Baghdadi and Al-Mathal, 2010). In addition, Mirazid showed therapeutic effect for *Giardia lamblia* infected rats, and produced a 100% reduction of intestinal and fecal parasitic counts (Fathy, 2011).

Not only dose the resin of this genus displays antimicrobial potential (Termentzi et al., 2011), but also the leaf, stem and bark are active against microorganism. Paraskeva et al. (2008) have studied antimicrobial potential of the leaf and stem extracts of ten *Commiphora* against four bacteria and two yeasts. The bark extracts of *C. berryi* and *C. caudata* displayed good inhibition on *Pseudomonas aeruginosa* (Kumari et al., 2011a). Inhibitory effects of *C. swaymertonii* on bacteria and fungus have been investigated by Bakari et al. (2011). The sesquiterpenes epicurzerenone and (1E)-8,12-epoxygermacra-1,7,10,11-tetraen-6-one (37) exhibited inhibitory activity against *Fusarium culmorum*, *Pythophthora cryptogaea* and *Alternaria solani* (Fraternali et al., 2011). Mansum-binoic acid (30) possessed potent antibacterial activity against a multidrug-resistant strain *Staphylococcus aureus* with a MIC value of 4 μg/mL (Rahman et al., 2008). A mixture of furanodiene-6-one (38) and 2-methoxyfuranogaua-9-ene-8-one (39) exhibited antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*, with MIC values ranging from 0.18 to 2.8 μg/mL (Dolara et al., 2000). The CHCl₃ inner bark extract of *C. schimperi* displayed antimalarial activity in vitro with an IC₅₀ value of 4.63 μg/mL (Koch et al., 2005).

4.5. Hepatoprotective activity

The reduced glutathione, glutathione S-transferase and glu- tathione peroxidase activities in PbA intoxication rabbit model recovered when treated with the resin of *C. molmol* (Ashry et al., 2010). Pretreatment with the resin of *C. opobalsamum* could shorten the barbiturate sleeping time and replenish the non- protein sulfhydryl of liver caused by CCl₄-induced live damage (Al-Howiriny et al., 2004a). The MeOH bark extract of *C. berryi* attenuated the increased levels of AST, ALT, ALP and serum bilirubin, activated SOD, catalase and glutathione peroxidase, and reduced the fatty degeneration and necrosis in CCl₄-induced hepatic injury model in rats (Gowri Shankar et al., 2008).

4.6. Antioxidant activity

Singlet oxygen was an actor of lipid peroxidation and DNA degradation, and a potential reason for the damage of cells. The essential oil of *C. myrrha* exhibited potent singlet oxygen quenching activity better than the control a-tocopherol. This effect was attributed by the reaction between furan ring of *C. myrrha* constituents (particular the furanosesquiterpenoids) and singlet oxygen (Racine and Auffray, 2005). Three furanosesquiterpenoids (27-29) from *C. myrrha* showed DPPH radical scavenging activity with EC₅₀ values of 1.08, 4.29 and 2.56 μg/mL (Fraternali et al., 2011).

The stem extracts of *C. tenuipetiolata*, *C. neglecta* and *C. mollis* showed antioxidant activity in ABTS assay with IC₅₀ values of 5.10, 7.28 and 8.82 μg/mL (Paraskeva et al., 2008). While the stem extract of *C. schimperi*, *C. neglecta*, *C. tenuipetiolata*, *C. edulis*, *C. berryi* and *C. caudata* exhibited antioxidant effect in the DPPH assay, with IC₅₀ values between 7.31 and 26.92 μg/mL (Paraskeva et al., 2008; Kumari et al., 2011a).

4.7. Hypolipidemic activity

Gugulipid, a standardized resin extract of *C. mukul*, has been sold in the market for the treatment of hyperlipidemia. Ulbricht et al. (2005) has summarized the hypolipidemic results of the *C. mukul* resin before 2003. Herein we focused the literature published since the previous review.

The resin of *C. mukul* and the active guggulsterone were inhibitors of low density lipoprotein (LDL) oxidation, and benef- ficial for the treatment of atherogenesis (Wang et al., 2004). It decreased the cholesterol and triglyceride (TG) levels, and increased the SOD activity on hypercholesterolemic rabbit model (Khanne et al., 2010). Administration of guggulipid (50 mg twice a day), the total cholesterol, LDL, TG, and the total cholesterol/high density lipoprotein (HDL) ratio decreased (Singh et al., 1994). A clinical study exhibited that gugulipid (containing 2.5% guggul- sterones) increased the LDL level, but had no impact on the level of cholesterol, HDL, TG and very-low-density lipoprotein (VLDL) (Szapary et al., 2003). However, a conflict clinical result reported that total cholesterol and HDL content decreased significantly when treated by gugulipid, and no changes of LDL and TG contents were found between the placebo and control groups (Nohr et al., 2009). Above different results might be caused by administration of different *C. mukul* materials.

There is no doubt that guggulsterones (21 and 22) are the most potent hypolipidemic substances in the *C. mukul* resin (Ramawat and Merillon, 2008). Their potent hypolipidemic property is based on the inhibition of the farnesoid X receptor (FXR), a nuclear hormone receptor activated by bile acids (Urizar et al., 2002). The cerebrane diterpenoids (25-26 and 40-41) and verticillane diter- penoids (42) from the same species suppressed the cholate-activated rate of human pancreatic IB phospholipase A2 (PLA2), which controls gastrointestinal absorption of fat and cholesterol (Yu et al., 2009). The combined hypolipidemic activities of guggulsterones targeting on FXR and cerebrane diterpenoids targeting on PLA2 accounted for the potent hypolipidemic activity of *C. mukul* resin.

4.8. Hypotensive activity and cardiac protection

Treated with the *C. mukul* extract, the increased heart rate and left ventricular end diastolic pressure, decreased arterial pressure, and altered myocardial contractility indices caused by myocardial ischemic impairment were prevented, and the cardiac function have been improved (Ojha et al., 2008). Intravenous administration of aqueous branch extract of *C. opobalsamum* decreased systemic arterial blood pressure and heart rate of anaesthetised rats. This hypotensive function was exerted though the activation of muscarinic cholinergic receptors (Abdul-Ghani and Amin, 1997).

4.9. Antidiabetic activity

Bellamkonda et al. (2011) reported antihyperglycemic and antioxidant effects of the ethanol resin extract of *C. mukul* in streptozotocin-induced diabetic rat model, which were benefit for the treatment of diabetes. As the major constituent of *C. mukul* resin, guggulsterones (21 and 22) prevented the impairment of glucose-stimulated insulin secretion, and protected the normal physiological function of pancreatic ß cells (Lv et al., 2008). A depth in vivo study revealed that 21 and 22 reduced the level of the blood glucose and plasma insulin, and increased the glycoen content in high fat diet induced type II diabetic models. The function of G6Pase, an important antidiabetic target, has been interfered by 21 and 22 (Sharma et al., 2009).
4.10. Antiulcer activity

The aqueous extract of *C. molmol* resin provided dose-dependent anti-ulcer and gastric mucosa protective effects in 80% ethanol, NaCl, NaOH and indomethacin induced ulcer model in rats. The necrosis, erosion, congestion and haemorrhage of the stomach wall caused by 80% ethanol were improved by pretreatment with *C. molmol* extract (Al-Harbi et al., 1997). The resin extracts of *C. opobalsamum* and *C. berryi* displayed similar protective effects in different mice ulcer models (Al-Howiriny et al., 2005; Gowrishankar et al., 2004). These data are consistent with its use for treatment of stomach diseases in traditional medicines.

4.11. Miscellaneous bioactivities

The resin of *C. mukul* ameliorated 6-n-propyl-2-thiouracil induced hypothyroidism in female mice model. The values of lipid peroxidation decreased, while SOD and catalase activities increased by treating with the resin extract of *C. mukul* at a dose of 200 mg/kg/d (Panda and Kar, 2005). Z-guggulsterone (21), the bioactive constituent of the *C. mukul* resin, increased the iodine uptake by thyroid, and enhanced the thyroid peroxidase and protease activity in vivo (Tripathi et al., 1984).

T-cadinol (43) from the resin of *C. guidotti* exhibited smooth muscle relaxing effect on the isolated guinea pig ileum and an inhibition on chola toxin-induced intestinal hypersecretion in mice (Claeson et al., 1991). 4(15)-eudesmen-1-β,6z-diol (44), (-)-oplopanone (45), and 6β,10β-dihydroxy-4(15)-guaiene (46) from the same species displayed smooth muscle-relaxing properties, but weaker than T-cadinol (Andersson et al., 1997).

Saxena et al. (2007) reported that the EtOAc extract of *C. mukul* resin had significant protection for streptozotocin-induced memory deficit in rat because of its acetylcholinesterase inhibitory and antioxidant properties. A series of sesquiterpenoids from *C. myrrha* showed neuroprotective effects against MPP⁺-induced neuronal cell death in H-SY5Y cells (Xu et al., 2011a,b). A mixture of 38 and 39 possessed anaesthetic activity by blocking the inward sodium current of excitable mammalian membranes (Dolar et al., 2000).

4.12. Toxicity

A goat was poisoned and eventually died from the oral administration of *C. myrrha* resin at a dose of 1–5 g/kg/d. The safe dose of the resin was suggested to be 0.25 kg/d (Omer and Adam, 1999). Side effects of the extract of *C. mukul* resin have been observed including mild gastrointestinal discomfort, possible thyroid problems and generalized skin rash (Nohr et al., 2009). The volatile oil of myrrh has pungent for skin, respiratory and digestive systems, and leading to allergy, nausea and decrease in locomotor activity (Li et al., 2008; Rao et al., 2001). That is the reason why myrrh is pre-treated with heat to reduce the volatile oil content before prescription in traditional Chinese medicine (Chen et al., 2010; Zhang and Zhu, 2005). The resin of *C. erlangeriana* is poisonous to humans and animals, and used for arrow poison in Eastern Africa (Habtemariam, 2003).

5. Conclusions

The present review discusses the phytochemical and pharmacological aspects of the genus *Commiphora*, and especially provides a detailed analysis of the literature published since the year of 2000. Terpenoids were regarded as the major constituents in this genus, while flavonoids and lignans commonly occurred in the bark or stem. Steroids and polypodane triterpenoids, characteristically present in the resin of *C. mukul*, might be important chemotaxonomic markers to identify *Commiphora* plant species from the phytochemical point of view.

Pharmacological studies carried out on crude extracts and pure metabolites provided pragmatic documents for its traditional uses, and have revealed this genus to be a valuable source for medicinally important molecules. Regarding the constituents contributed to medicinal values, the findings indicated that triterpenoids and diterpenoids are mainly responsible for anti-inflammatory property, sesquiterpenoids for antimicrobial, smooth muscle-relaxing and analgesic effects, lignans for the cytotoxic and toxicity, and steroids for antiproliferative, anti-inflammatory, hypolipidemic and anti-diabetic activities. Guggulsterones (21 and 22) displayed potent inhibitory effect on tumor cells *in vitro* and *in vivo*, as well as anti-inflammatory property *in vivo*. Myrrhanol A (23), a polypodane triterpenoid from *C. mukul*, exhibited more potent anti-inflammatory effect than hydrocortisone in adjuvant-induced air pouch granuloma model. Hence, 21, 22 and 23 have the potential to be developed as antitumor and anti-inflammatory agents. Above three compounds only occur in the resin of *C. mukul*, and this finding supports its traditional uses in Ayurvedic medicine as an anti-inflammatory agent.

Throughout our literature review we observed that different *Commiphora* species were inclined to dissimilar pharmacological functions. The resin of *C. mukul* possesses potent anti-inflammatory and hypolipidemic effects targeting cardiovascular diseases, and has been developed as hypolipidemic agent. The resin of *C. molmol* is good at the treatment of ulcer and diseases induced by microbial infections, its crude extract has been sold in the market as an antiparasitic drug. The resin extracts of *C. opobalsamum* and *C. berryi* exhibit protection on ulcer and hepatotoxicity in mice. The resin of *C. myrrha* is expertized in relieving the pain. These outcomes validate the ethnomedical uses of *Commiphora* species in different regions, however, a serious flaw exists in the pharmacological studies. Most of the plant material used in above bioassay was not well characterized, and this defect led to the difficulty to reproduce the reported results. To add the availability of primary experimental data, identification and quantification of bioactive substances and standardization of extracts are conducted prior to the pharmacological test.

The toxicity of *Commiphora* species is limited, mainly involving in the allergy, nausea and decrease of locomotor ability attributed by volatile oil. The resin of *C. erlangeriana* is a more toxic material because it contains lignans poisonous to human.

In order to further develop the medical uses of *Commiphora* species some research questions need to be addressed. Former research of this genus focused on the resinous exudates, and other plant tissue should be paid more attention, for example, stem, bark and leaf. Expansion of research materials would provide more chances for discovery of new bioactive principle from the genus *Commiphora*. Validating the correlations of the ethnomedical uses, bioactive substances and pharmacological effects is of special importance, and is still the primary task for future research. Efforts are also needed to detailedy investigate the physiological and biochemical functions demonstrated by these species, identify the individual bioactive natural products, and illustrate their mechanism of action. The current results are largely limited to *in vitro* bioassay, and *in vivo* studies using laboratory animals are needed. Furthermore, the promising results confirmed by animal models should be further investigated by clinical trials. Suitable analytical and standardization protocols of plant materials should be developed, since these are the groundwork for convincing and reproducible pharmacological studies.
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Appendix A  Supporting information

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References


