Chapter 11
Pharmacological Applications of Lucidone: A Naturally Occurring Cyclopentenedione

K.J. Senthil Kumar and Sheng-Yang Wang

Abstract *Lindera erythrocarpa*, commonly known as spicewood or spicebush, has a long history of use as a traditional remedy and culinary spice. Recent studies have reported that lucidone, an active constituent of fruits and leaves of *Lindera erythrocarpa*, has various beneficial properties, such as antioxidant, anti-inflammatory, hepatoprotective, dermatoprotective, hypolipidemic, and skin-whitening effects. The pleiotropic activities of lucidone derive from its unique chemistry as well as its ability to modulate multiple signaling pathways, such as inflammatory signaling pathways regulated by NF-κB and MAPKs; cytoprotective pathway that depends on Nrf2 activation and inhibition of apoptosis; hypolipidemic pathway regulated by PPRγ and C/EBPα; and anti-melanogenic pathway modulated by MITF. Also, lucidone is remarkably low cytotoxic and exhibits limited bioavailability. These findings suggest that lucidone is a promising agent for the treatment of inflammatory and oxidative diseases.

Keywords Anti-inflammation • Anti-melanogenesis • Dermatoprotection • Hepatoprotection • Hypolipidemic • *Lindera erythrocarpa* • Lucidone

Abbreviations

AAPH	2,2′-Azobis(2-amidinopropane) dihydrochloride
ALT	Alanine aminotransferase
AP-1	Activator protein-1
ARE	Antioxidant response element
AST	Aspartate aminotransferase

K.J. Senthil Kumar
Department of Forestry, National Chung Hsing University, Taichung, Taiwan

S.-Y. Wang (✉)
Department of Forestry, National Chung Hsing University, Taichung, Taiwan

Agricultural Biotechnology Research Center, Academia Sinica, Taipei, Taiwan
e-mail: taiwanfir@dragon.nchu.edu.tw

© Springer Science+Business Media Singapore 2016

H.-S. Tsay et al. (eds.), *Medicinal Plants - Recent Advances in Research and Development*, DOI 10.1007/978-981-10-1085-9_11

ATF-2	Activating transcription factor-2
cAMP	Cyclic adenosine monophosphate
COX-2	Cyclooxygenase-2
EMSA	Electrophoretic mobility shift assay
ERK	Extracellular signal-regulated kinase
GSH	Glutathione
HF	High fat
HO-1	Heme oxygenase-1
IκB	Inhibitor of nuclear factor kappa-B
IKK	IκB kinase
iNOS	Inducible nitric oxide synthase
JNK	c-JUN N-terminal kinase
LDH	Lactate dehydrogenase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
MITF	Microphthalmia-associated transcription factor
MKK	Mitogen kinase kinase
NAFLD	Nonalcoholic fatty liver diseases
NF-κB	Nuclear factor kappa-B
NO	Nitric oxide
Nrf2	Nuclear factor E2-related factor-2
PGE_2	Prostaglandin-E_2
PPARγ	Peroxisome proliferator-activated receptor-γ
ROS	Reactive oxygen species
SAPK	Stress-activated protein kinase
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor alpha
TRP	Tyrosinase-related proteins
UVA	Ultraviolet A
α-MSH	Alpha-melanocyte-stimulating hormone

11.1 Introduction

Phytochemicals, nonnutritive components existing in fruits, vegetables, edible macrofungus, algae, and bacteria, are increasingly gaining popularity over conventional synthetic drugs, primarily because they act via multiple molecular targets, which synergize to prevent efficiently or treat chronic disorders. Phytochemicals are safe with nontoxic or minimal toxic side effects with better bioavailability. It is known that the metabolism of plants is divided into two major types: primary and secondary. The substances that are common to living things and essential to cell maintenance such as lipids, proteins, carbohydrates, and nucleic acids are originated from

the primary metabolism. Moreover, substances originated from several biosynthetic pathways that are restricted to determined groups of organisms are results of the secondary metabolism including, polyphenols, alkaloids, terpenes, steroids, saponins, flavonoids, lignans, tannins, cyclopentene diones, polysaccharides, fatty acids, and organic acids. Given the great structural diversity of phytochemicals, it is not feasible to define the structure-activity relationship to deduce their underlying molecular mechanisms. A better approach is to elucidate their medicinal properties by analyzing modulations in signal transduction pathways.

Cyclopentenediones (CPDs) are secondary metabolites found in higher plants, fungi, algae, and cyanobacteria. A common denominator of CPDs is the cyclopent-4-ene-1,3-dione skeleton with various functional groups. Most of the CPDs were primarily isolated from plants or macrofungus, although synthetic analogs with new biological properties and greater pharmacological efficacies were subsequently studied (Sevcikova et al. 2014). There are several pharmacologically important CPDs that have been investigated. Coruscanones A and B isolated from *Piper coruscans* exhibit potent antifungal properties (Babu et al. 2006). Asterredione isolated from *Aspergillus terreus* occurring in the rhizosphere of *Opuntia versicolor*, using bioassay-guided fractionation and the cytotoxic evaluation with a panel of three sentinel cancer cell lines, NCI-H460 (non-small cell lung cancer), MCF-7 (breast cancer), and SF-268 (CNS glioma), showed a moderate cytotoxic effects (Wijeratne et al. 2003). Involutone was isolated from the mushroom *Paxillus involutus* using ethanol, methanol, or n-butanol extracts (Antkowiak et al. 2003). Nostotrebin 6, a bis-cyclopentenedione isolated from a methanol extract of the cyanobacterial strain *Nostoc* sp. str. Lukesova 27/97, significantly inhibited acetylcholinesterase and butyrylcholinesterase activities with an IC_{50} value of 5.5 μM and 6.1 μM, respectively (Zelik et al. 2010). Linderone, methyllinderone, lucidone, and methyllucidone isolated from ethyl acetate extracts of fruits of *Lindera erythrocarpa* and lucidone exhibited potent anti-inflammatory effect against lipopolysaccharide-induced inflammation in murine macrophages RAW264.7 cells in vitro (Wang et al. 2008). Subsequent investigations with lucidone showed antioxidant (Kumar et al. 2013), anti-inflammatory (Senthil Kumar et al. 2010; Senthil Kumar and Wang 2009), anti-melanogenic (Kumar et al. 2010), hepatoprotective (Chen et al. 2013; Senthil Kumar et al. 2012), and hypolipidemic (Hsieh and Wang 2013) effects. In addition, methyllucidone showed a significant inhibition of farnesyl protein transferase and antitumor activity in various human cancer cell lines in vitro (Oh et al. 2005). Fermentation extracts of *Streptomyces* strain, K93-0711, produced madindolines A and B which displayed a dose-dependent inhibition of MH60 cells, an interleukin-6 (IL-6)-dependent cell line, whereas these compounds did not show any antimicrobial activities (Yang et al. 2013). Moreover, synthetic analogs of cyclopentenedione-derived TX-1123 and TX-1925 showed antitumor activity through the inhibition of protein tyrosine kinase activities (Surh et al. 2000). G2201-C, a cyclopentenedione antibiotic produced by *Streptomyces cattleya*, was found to be moderately active in vitro against Gram-positive bacteria, weakly active against Gram-negative bacteria, and inactive against fungi. Also, G2201-C was toxic to mice (Noble et al. 1978). Chrysotriones A and B, two 2-acylcyclopentene-

1,3-dione derivatives isolated from the fruiting bodies of Basidiomycete *Hygrophorus chrysodon*, showed antifungal activity against *Fusarium verticillioides* (Tichotova et al. 2011). A large number of CPDs have been shown to possess antibacterial and antifungal properties, despite recent studies indicating that CPDs are potent anti-inflammatory, hepatoprotective, and neuroprotective agents (Sevcikova et al. 2014). Among the known CPDs, lucidone is the most extensively studied. This chapter provides comprehensive information on the biological effects and pharmacological importance of lucidone.

11.2 Source, Isolation, Chemical Properties, and Synthesis of Lucidone

11.2.1 Source of Lucidone

Many species in the *Lauraceae* family have been used in folk medicine and culinary purposes. The genus *Lindera* belonging to Lauraceae is one of the economically important genera commonly known as spicewood, spicebush, and Benjamin bush. The Latin name *Lindera* commemorates the Swedish botanist Johan Linder (1676–1724). *Lindera* species widespread in Eastern Asia and few in Northern America have several important medicinal plants including *L. lucida*, *L. erythrocarpa*, *L. aggregata*, *L. glauca*, *L. obtusiloba*, *L. reflexa*, *L. akoensis*, *L. oxyphylla*, *L. umbellata*, *L. melissifolia*, *L. pulcherrima*, *L. communis*, *L. neesiana*, *L. fruticose*, *L. angustifolia*, *L. chunni*, and *L. strychnifolia. L. erythrocarpa* Makino (Fig. 11.1A) is an important species distributed mainly in Eastern Asia including Taiwan, Japan, Korea, and China (Oh et al. 2005). The fruits of *L. erythrocarpa* are used as a folk medicine for analgesic, digestive, diuretic, antidote, and antibacterial activities (Wang et al. 2008).

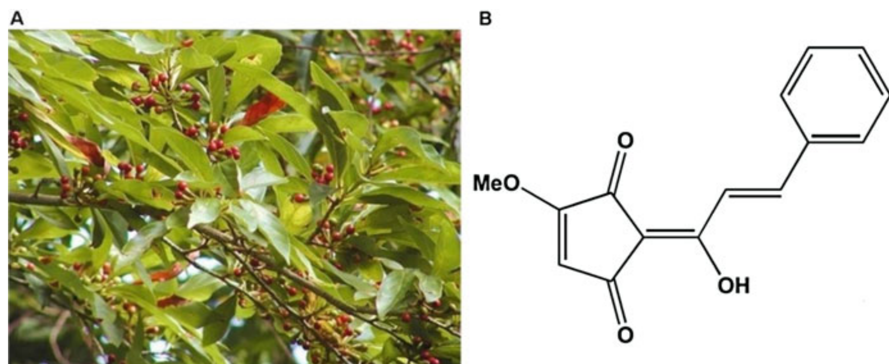

Fig. 11.1 (**A**) Fruits of *Lindera erythrocarpa* Makino. (**B**) Chemical structure of lucidone

The genus *Lindera* is one of the major sources of naturally occurring cyclopentenedione such as linderone, methyllinderone, lucidone, and methyllucidone. Lucidone (Fig. 11.1B) was first isolated in 1968 from the fruits of *Lindera lucida* (Syn. *L. malaccensis* or *L. selangorensis*) using chloroform extracts (Comai et al. 2010). The obtained yellow crystalline compound was immediately identified as lucidone, and the structure indicated that lucidone exhibits cyclopent-4-ene-1,3-dione tautomerism. The detailed study on the structure of lucidone was carried out by Ng et al. (1990). They reported that external tautomers exist in lucidone through strong intramolecular hydrogen bonding (Ng et al. 1990). After over three decades, lucidone was subsequently isolated from other relative species such as *Lindera erythrocarpa* Makino (Wang et al. 2008).

11.2.2 Isolation and Chemical Properties of Lucidone

The dried fruits of *L. erythrocarpa* Makino (2 kg) were extracted with EtOH. The total crude extract was concentrated under vacuum to yield a residue (124.3 g). One hundred grams of EtOH crude extract was suspended in H_2O in the ratio of 1:1 and successively partitioned with n-hexane (n-hex) and ethyl acetate (EA), yielding n-hex soluble fraction (16.0 %), EA-soluble fraction (45.6 %), and EA-insoluble fraction (34.3 %). The EA-soluble fraction (15 g) was chromatographed on a silica gel column, eluted with a gradient of n-hex/EA (95/5–100/0) to give a total of 12 subfractions (EA-1 to EA-12). When EA subfraction-5 (EA-5) was further separated by semi-preparative HPLC using Cosmogel column, eluted with n-hex/dichloromethane/EA solvent system, it resulted into four major compounds: linderone, methyllinderone, lucidone, and methyllucidone (Wang et al. 2008). The structures of these four compounds were confirmed by spectroscopic analyses. The amount of lucidone in the EtOH extract was further analyzed by HPLC. It was found that the total content of lucidone was 6.50 % in the EtOH extract of *L. erythrocarpa* Makino fruits (Wang et al. 2008).

Lucidone((2Z)-2-[(2E)-1-hydroxy-3-phenylprop-2-en-1-ylidene]-4-methoxycyclopent-4-ene-1,3-dione) is a yellow powder, soluble in organic solvents such as dimethyl sulfoxide (DMSO), EtOH, MeOH, or acetone and has a melting point of 166.5–168.5 °C. Its molecular formula is $C_{15}H_{12}O_4$, and the molecular weight is 256.0752 g/mol. Accurate mass measured that was analyzed by high-resolution electron impact mass spectrometry (HREIMS) resulted in [M] + m/z 256.0752. Its chemical formula is $C_{15}H_{12}O_4$ (calcd m/z 256.0735). ^{1}H NMR ($CDCl_3$): δ 3.96 (s. 3H), 7.40 (m, 3H), 7.63 (m, 3H), and 7.71 (d, 1H, *J* = 18 Hz) (Oh et al. 2005).

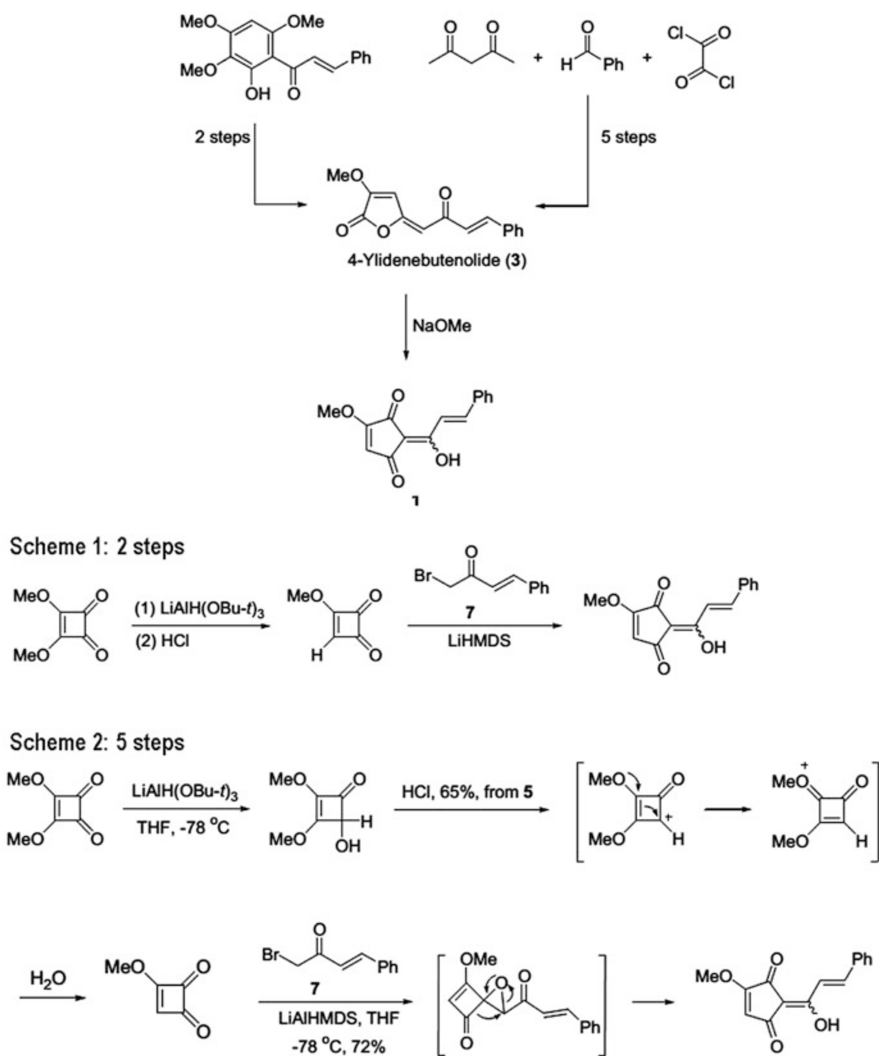

Fig. 11.2 Concise synthesis of lucidone (Adapted from Wu et al. 2013)

11.2.3 Synthesis of Lucidone

As lucidone exhibits various pharmacological properties, it was chemically synthesized by various research groups. Wu et al. (2013), utilized "one-pot" reduction/rearrangement of dimethyl squarate and Darzens/ring expansion of the monomethoxy cyclobutenedione. The synthesis of lucidone was accomplished in two steps and obtained 46 % total yield (Zhao et al. 2006). A concise synthesis of lucidone is depicted in Fig. 11.2.

11.3 Pharmacological Properties of Lucidone

Accumulating evidence suggests that lucidone has a diverse range of pharmacological properties such as anti-inflammatory, antioxidant, hepatoprotective, neuroprotective, dermatoprotective, and skin-whitening effects through the modulations in molecular targets, supporting the notion that it acts upon various biochemical and molecular cascades. Lucidone modulates various targets either through direct interaction or via modulation of gene expression. Various molecular targets modulated by lucidone include transcription factors, growth factors, and their receptors, cytokines, enzymes, and genes regulating inflammation and oxidative stress.

11.3.1 Anti-inflammatory Activities

Inflammation is a complicated and crucial physiological response to many pathological conditions including tissue injury and microbial invasion, which is manifested with redness, swelling, and pain. Macrophages play a functional role in coordinating the immune response to invading pathogens through phagocytosis and cytokine secretion. Activation of macrophages by endotoxins or pathogenic microorganisms produces a vast amount of pro-inflammatory molecules including nitric oxide (NO), prostaglandin E_2 (PGE_2), tumor necrosis factor-α (TNF-α), and interleukin-1β/6 (IL-1β/6) (Joshi and Mathela 2012). The constant production of these molecules involves a variety of inflammatory disorders, such as rheumatoid arthritis, atherosclerosis, asthma, hepatitis, pulmonary fibrosis, and cancer. Therefore, inhibition of these pro-inflammatory molecules represents an ideal target for minimizing the burden of inflammatory diseases (Joshi and Mathela 2012).

The production of pro-inflammatory molecules was mediated by a variety of soluble factors and signaling events. For example, NF-κB-dependent gene expression plays a crucial role in inflammatory responses and increases the expression of genes encoding inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). TNF-α and IL-1β are enzymes involved in the synthesis of NO, PGE_2, TNF-α, and IL-1β, respectively. Under the normal physiological condition, NF-kB is sequestered in the cytoplasm by complex with its negative regulator, inhibitor κBs (IκBα, IκBβ, and IκBγ). Upon activation of IκBs by their upstream kinase, inhibitor κB kinase (IKKα), NF-κB is disassociated and exported to the nucleus, where its target genes may be activated (Joshi and Mathela 2012).

Clinically used anti-inflammatory drugs exhibit several side effects on humans and a high cost of treatment, as in the case of biologics. Natural products derived from anti-inflammatory agents offer promising options for the development of drugs for treating inflammatory diseases. Although, for centuries, herbal products have been utilized to treat or minimize the inflammatory disorders, the most successful

example is curcumin from the tuber of *Curcuma longa* (turmeric). The anti-inflammatory activity of *L. erythrocarpa* was evaluated in vitro through measuring NO production from LPS-stimulated macrophages (Wang et al. 2008; Senthil Kumar and Wang 2009). Our findings showed that EA-soluble fraction derived from EtOH extracts of *L. erythrocarpa* fruits exhibited potent NO inhibitory effect. Also, four cyclopentene diones, namely, linderone, methyllinderone, lucidone, and cis/trans-methyllucidone, were identified as major compounds of this active fraction. In further analysis with the bioactivity-guided fraction procedure, lucidone showed a strong NO inhibitory activity with an EC_{50} value of 4.22 μg/mL (Wang et al. 2008). Also, lucidone significantly inhibited the secretion of PGE_2 and TNF-α in LPS-induced murine macrophage RAW264.7 cells. Further analysis with immunoblotting and Q-PCR revealed that the inhibition of pro-inflammatory molecules occurred through the downregulation of their corresponding mediator genes, iNOS and COX-2. Electrophoretic mobility shift assay (EMSA) and Western blotting suggested that the inhibition of pro-inflammatory genes by lucidone is caused by the suppression of nuclear export and transcriptional activation of the redox-sensitive transcription factor, NF-κB. Also, lucidone increased the protein stability of the IκBα, an endogenous repressor of NF-κB, through the inhibition of its phosphorylation and proteasomal degradation. It was found that lucidone significantly blocked the LPS-induced IKKα, an upstream kinase of the IκBα (Senthil Kumar and Wang 2009). These reports strongly suggest that lucidone inhibits production of pro-inflammatory molecules through the suppression of the redox-sensitive NF-κB signaling pathway (Fig. 11.3).

Though the role of NF-κB signaling pathway in inflammation is well characterized, however, only a few studies have reported the alternative inflammatory signaling pathway such as activator protein 1 (AP-1) pathway. AP-1, an early transcription factor, regulates iNOS and COX-2 expression in macrophage cells, either alone or in association with NF-kB. Lee et al. (2007) reported that mitogen-activated protein kinases (MAPKs) including p38 MAPK, JNK/SAPK, and ERK1/2 trigger transcriptional activation of AP-1. The LPS-induced activation of MAPKs, particularly p38 MAPK and JNK/SAPK, was significantly prevented by lucidone in a dose-dependent manner. Furthermore, lucidone treatment inhibited the nuclear translocation and transcriptional activity of ATF-2 (a member of AP-1 family in LPS-induced macrophages) in vitro (Senthil Kumar and Wang 2009) (Fig. 11.3).

Subsequent in vivo studies have shown that lucidone protects mice from acute inflammation (Senthil Kumar et al. 2010). Acute systemic inflammation in male ICR mice was induced by injection of LPS (5 μg/kg), and the protective effect of lucidone (50–200 mg/kg) was determined by measuring the production of pro-inflammatory molecules. Lucidone treatment strongly reduced NO, PGE_2, and TNF-α levels in mice blood serum. Protein and mRNA analyses of the liver samples confirmed that lucidone inhibited the production of pro-inflammatory molecules through the downregulation of their corresponding mediators, iNOS and COX-2, followed by the suppression of transcriptional activation of NF-κB and AP-1 signaling pathways (Senthil Kumar et al. 2010). In another study, lucidone was proved to be effective against inflammation in a rodent model. A topical application of

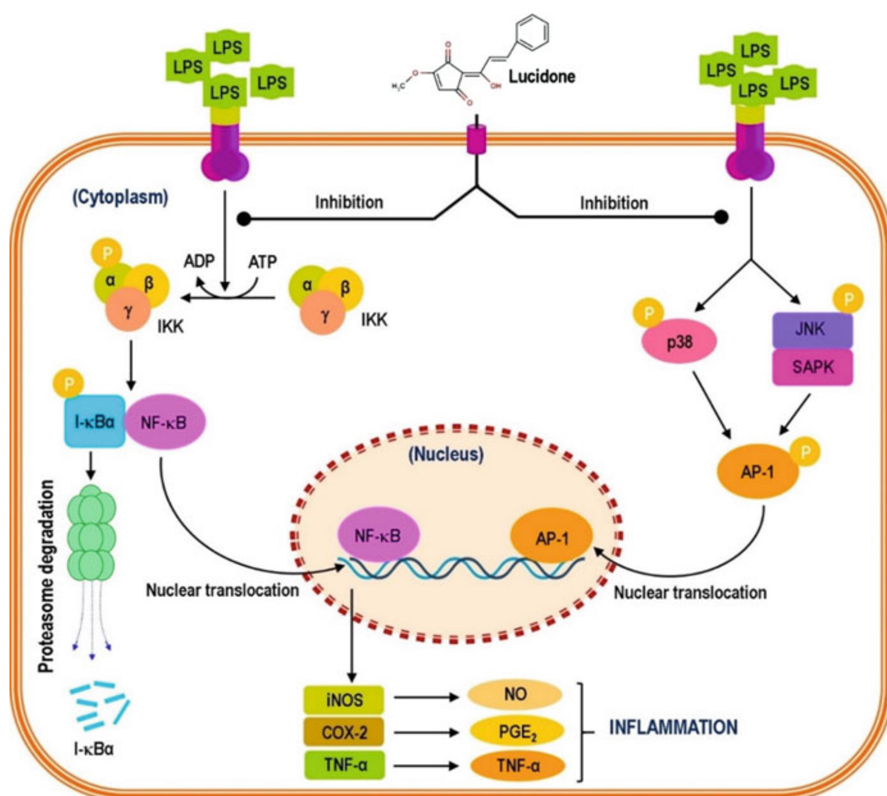

Fig. 11.3 Schematic depiction of the anti-inflammatory mechanism of lucidone

lucidone at a dose of 0.5 and 1 mg/ear significantly reduced croton-oil-induced ear edema in mice. The percentage of edema reduction in treated mice was 44 % and 25 %, respectively (Wang et al. 2008). These reports concluded that lucidone exerted anti-inflammatory effects by inhibiting the expression of pro-inflammatory factors and their corresponding transcriptional factors (Fig. 11.3).

11.3.2 Hepatoprotective Activities

The liver is the prime organ which regulates many metabolic functions and plays an important role in the maintenance of an internal environment of the body through its multiple and diverse functions. The chronic liver diseases represent a global concern. There is a progressive increase in the incidence of hepatic damage mainly due to viral infection, hepatotoxic chemicals (alcohol), toxin in food (especially aflatoxins), peroxides (particularly peroxidized edible oil), pharmaceutical antibiotics,

chemotherapeutics, CNS active agents, environment pollutants, and xenobiotics. Among these, the excessive ingestion of alcohol plays a crucial role in the development of hepatic diseases such as alcoholic hepatitis and cirrhosis. Alcohol is absorbed rapidly in the gastrointestinal tract: 70 % in the small intestine, 20 % in the stomach, and the remaining in the colon. The absorbed alcohol is immediately (within 60 min) distributed to all the tissues, especially concentrated in greater proportion in the brain, blood, eye, and cerebrospinal fluid. Ethanol is eliminated mainly (>90 %) by the liver through the enzymatic oxidation pathway; 5–10 % is excreted by the kidneys and lungs and in sweat. A number of studies have reported that ethanol-induced oxidative stress and inflammation produce vast amounts of cytokines and chemokines, especially NO, TNF-α, transforming growth factor-beta (TGF-β), and reactive oxygen species (ROS). These are believed to play a major role in pathogenesis and progression of alcoholic liver diseases. Particularly, the overproduction of ROS during alcohol metabolism is an inevitable phenomenon associated with alcoholic liver diseases. A basal level of ROS is generated during normal cellular metabolism; however, cells exposed to toxins or free radical generators produce vast amounts of ROS, which induce lipid peroxidation, protein degradation, and DNA damage.

Over the past four decades, mounting evidence has shown that dietary phytochemicals are the promising alternative medicine in preventing oxidative stress-related liver diseases and protecting cells from toxicity. It was found that lucidone possesses a potent protective activity against the alcohol-induced hepatotoxicity through the induction of antioxidant enzymes and regulatory factors which counteract the cytotoxic effect of alcohol. An acute hepatotoxicity in human hepatic cells (HepG2) was induced by exposure to ethanol (100 mM), and the protective effect of lucidone was determined by pretreatment of cells with increasing concentrations of lucidone (1–10 μg/mL) for 2 h. The notable signs of ethanol-intoxicated hepatic injury are leakage of hepatic transaminases and cytokines into the circulatory system. Serum biochemical analysis shows that the ethanol-induced increase in the production of alanine aminotransferase (ALT) and aspirate aminotransferase (AST) was significantly inhibited by lucidone in a dose-dependent manner without appreciable cytotoxic effects. The crucial role of pro-inflammatory cytokines and chemokines such as NO, TNF-α, and IL-1β in the development of alcoholic liver diseases has been well demonstrated (Zhao et al. 2015). Especially, TNF-α is of great relevance to liver pathology, as increased enzyme levels and protein expression were observed in many forms of liver diseases, such as alcoholic liver diseases. Also, it mediated hepatocyte apoptosis (Fernandez-Checa et al. 2005). Fernández Checa et al. (2002) reported that mice deficient in TNF-a receptor (TNFR1) failed to develop alcoholic liver diseases except steatosis which indicates the crucial role of TNF-α in the alcoholic liver diseases. Therefore, controlled production of TNF-α primarily is implied to prevent alcoholic liver diseases in humans. It is noteworthy that pretreatment of hepatic cells with lucidone significantly prevented alcohol-induced TNF-α production. This observation was concomitant with a previous report that lucidone inhibits LPS-induced TNF-α secretion in macrophage cells. In addition to the pro-inflammatory cytokines, NO, a chemokine, has been demon-

strated as another key player of liver diseases (Chen et al. 2015). It was demonstrated that the exposure of human astrocytoma cells to ethanol increased NO production in vitro (Davis et al. 2002). Also, a mixture of pro-inflammatory cytokines induced NO production in human hepatocyte HepG2 cells (Majano et al. 2004). An in vivo study showed that acute or chronic alcohol exposure increased NO production in rat circulatory system (Deng and Deitrich 2007). However, in our study, for the first time, we reported an ethanol-induced NO production in HepG2 cells (Senthil Kumar et al. 2012), though pretreatment with lucidone significantly blocked the increase of NO production (Senthil Kumar et al. 2012). This data is in conformity with our previous report that lucidone inhibited LPS-induced NO production in murine macrophage cells (Senthil Kumar and Wang 2009). Reduced glutathione content is often used for the evaluation of oxidative stress in biological systems. Augmentation of GSH/GSSG ratio has been demonstrated to protect the liver from oxidative stress. In our earlier study, it has been reported that exposure of hepatic cells to ethanol significantly increased GSH depletion, whereas pretreatment with lucidone prevents such reduction in GSH protein levels (Senthil Kumar et al. 2012). During the alcohol metabolism, alcohol is oxidized into aldehydes, especially acetaldehydes (ADAs) and malonaldehydes (MDAs). Elevated MDA and decreased antioxidant capacities have been used as biomarkers of oxidative stress. Interestingly, pretreatment with lucidone significantly blocked ethanol-induced lipid peroxidation as evidenced by decreased malonaldehyde (MDA) level in HepG2 cells (Senthil Kumar et al. 2012).

Ethanol-mediated ROS generation plays a critical role in the development of alcoholic liver diseases and in limiting the expression of cytoprotective genes. Therefore, the removal of ROS accumulation through cellular antioxidant defense system could maintain the intracellular redox homeostasis. Lucidone pretreatment significantly prevented ethanol-induced intracellular ROS accumulation in cultured HepG2 cells (Senthil Kumar et al. 2012). Further cell-free antioxidant analysis such as DPPH and iron-chelating assays revealed that lucidone does not have the ability to directly scavenge free radicals. In such conditions, most of the eukaryotic cells are fortified with primary and secondary defense against oxidative stresses. Particularly, phase II enzymes such as heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), and glutathione-*S*-transferase (GST) get rapidly activated by an endogenous mechanism through which oxidative toxicants are removed before they could damage the DNA. Conversely, excessive or chronic oxidative stress increases weakened defense and reduces endogenous antioxidants. In these conditions, induction of antioxidant defense by external factors is an important component of the cellular stress response. Many natural products have been reported to have beneficial effects on alcoholic liver diseases: polyphenols, flavonoids, terpenoids, carotenoids, vitamins, silymarin, curcumin, *N*-acetylcysteine, and antroquinonol are well known for their high antioxidant contents. These components not only act as free radical scavengers but also modulate signal transduction pathways and gene expression patterns. Particularly, HO-1 is a rate-limiting enzyme that catalyzes heme into biliverdin, free iron, and carbon monoxide. Induction of HO-1 has been reported to minimize cellular injuries, oxidative stress, pro-

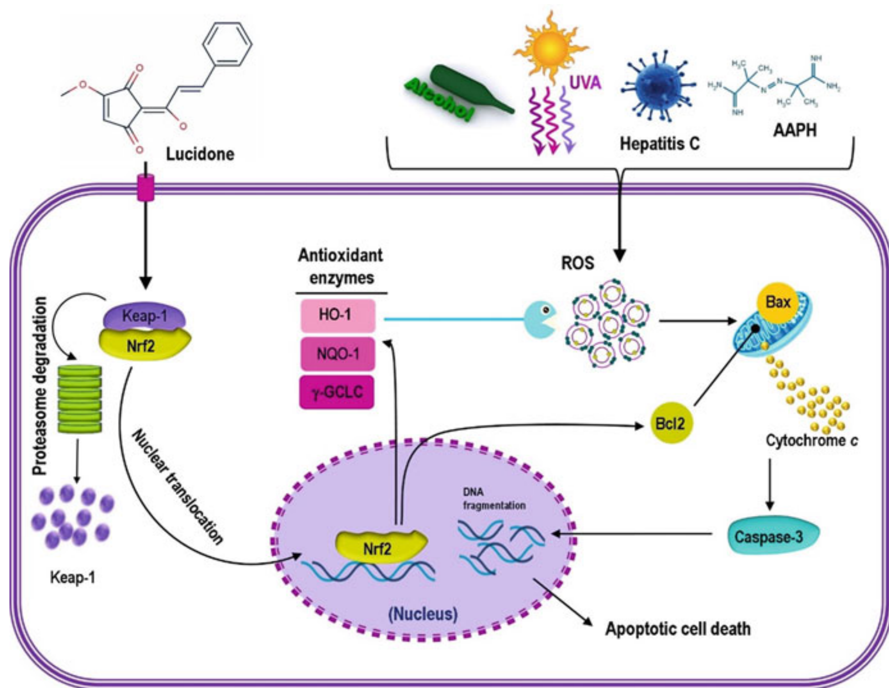

Fig. 11.4 Schematic diagram of the antioxidant defense mechanism or cytoprotective effects of lucidone

inflammatory cytokine production, and proapoptotic inducer activation (Braudeau et al. 2003). A recent study has reported that ethanol exposure prominently reduced the endogenous HO-1 level in hepatocytes (Bao et al. 2010). In our study, it was demonstrated that the ethanol-induced decline in HO-1 level was significantly prevented by lucidone in hepatic cells, while Surh (2003) reported that lucidone treatment significantly induced the transcriptional activation of Nrf2, a binding of redox-sensitive transcription activator to antioxidant response element (ARE) in the upstream promoter region of many antioxidant genes including HO-1 (Surh 2003). Previous studies also indicated that the increased Nrf2 activity in hepatic tissues is highly hepatoprotective during chemical- or ethanol-induced oxidative stress (Farombi et al. 2008; Yao et al. 2007). It is also found that lucidone-mediated induction of antioxidant genes, such as HO-1, is associated with the alcohol-induced oxidative stress (Fig. 11.4). These results suggest that lucidone could be a potential lead compound for the treatment of alcoholic liver diseases.

Hepatitis C virus (HCV) is one of the five known hepatitis viruses: A, B, C, D, and E. HCV is a leading causative agent of hepatocellular carcinoma (HCC) disease in developed countries, and it is estimated that 3 % of the world population is infected with this virus (Stauber and Stadlbauer 2006). To determine the potential

effects of lucidone on HCV replication, Ava5 cells, a parent Huh-7-derived cell line harboring an HCV sub-genomic RNA replicon, were treated with increasing concentration of lucidone (5–50 μM) for 4 days or a single dose (50 μM) for various time points (24–96 h). Results of Western blotting analysis showed that lucidone markedly decreased the HCV NS5B protein levels in a concentration- and time-dependent manner (Chen et al. 2013). Also, lucidone significantly suppressed HCV RNA levels with an EC_{50} value of 15 ± 0.5 μM. Next, the cell viability assay (MTS assay) revealed that lucidone is not cytotoxic at effective antiviral concentrations as indicated by 50 % cytotoxic concentration (CC_{50}) value of 620 ± 5 μM (Chen et al. 2013). In addition, HCV JFH-1 infectious assay confirmed the inhibitory effect of lucidone on viral RNA replication, with 50 % effective concentration (EC_{50}) of 20 ± 1.1 μM, which is an acceptable selectivity index (SI; CC_{50}/EC_{50}) of ~31. Also, treatment with lucidone significantly induced HO-1 expression and led to the increase of its product biliverdin for induction of antiviral interferon (INF) response and inhibition of HCV NS3/4A protease activity. Conversely, the anti-HCV activity of lucidone was barely observed in HO-1 or Nrf2 silenced cells, indicating that the anti-HCV property of lucidone was due to the induction of Nrf2-mediated HO-1 expression (Fig. 11.4). Moreover, co-treatment of lucidone with alpha interferon, the protease inhibitor telaprevir, the NS5A inhibitor BMS-790052, or the NS5B polymerase inhibitor PSI-7977 synergistically suppressed HCV RNA replication. These findings suggest that lucidone could be a potential lead or a supplement for the development of new anti-HCV agents (Chen et al. 2013).

11.3.3 Hypolipidemic Activity

Obesity is a complex disorder involving an accumulation of excessive body fat. Its incidence is dramatically increasing in developed and developing countries due to diet and lifestyle changes. Overweight is defined as a body mass index (BMI) of 25–30 and obesity as a BMI >30, with the latter being classified into class I (BMI of 30–35), class II (BMI of 35–40), and class III (BMI >40). Obesity can also be differentiated between peripheral and central obesity, with the latter having more implication in the metabolism (Watt and Charlton 2010). According to the World Health Organization (WHO), the worldwide prevalence of obesity has nearly doubled between 1980 and 2008, and more than 10 % of the adults aged 20 and over were obese in 2008. Obesity increases the risk of developing various pathological conditions including insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, atherosclerosis, and nonalcoholic fatty liver diseases (NAFLD). Risk factors for the above are smoking, hypertension, serum cholesterol, genetic factors, physical activity, hormones, alcohol, and diseases related to the thyroid, kidney, and liver. Adipose tissue has been recognized as an active endocrine organ and a main energy store of the body. Extensive adipocyte remodeling by adipocyte hyperplasia (increased number of adipocytes), adipocyte hypertrophy (increased size of adipocytes), and angiogenesis (neovasculature) is the crucial factor involving obesity.

Excess fat accumulation from free energy intake such as high-fat diet promotes the release of free fatty acids into the circulation from adipocytes, and hyperplasia results from the complex interplay between proliferation and differentiation of preadipocytes. Increasing evidence suggests that natural products have the potential to suppress preadipocyte differentiation and adipogenesis in 3T3-L1 cells and prevent obesity in animal models. For example, curcumin, an active ingredient of turmeric (C*urcuma longa*), inhibited preadipocyte differentiation and blocked body weight gain in diet-induced obesity mice through the downregulation of lipogenesis in the liver (Ferguson et al. 2016). Berberine, an isoquinoline alkaloid isolated from the roots of *Berberis aristata*, inhibits adipocyte differentiation by suppressing PPARγ and reducing the secretion of adipogenic enzymes. Also, berberine reduced serum glucose level and body weight gain in high-fat-diet-induced mice and decreased lipid levels in the circulation of both obese and normal SD rats (Pang et al. 2015). In a similar way, epigallocatechin gallate inhibits preadipocyte differentiation through the suppression of PPARγ pathway via activating AMPK (Moon et al. 2007) and also attenuates fatty liver formation in diet-induced obese mice. These studies strongly suggest that natural products have the potential to inhibit preadipocyte differentiation in vitro and hypolipidemic effects in vivo. We recently reported that lucidone inhibited 3T3-L1 adipocyte differentiation by suppressing the transcription of master regulators of adipogenesis including PPARγ and C/EBPα (Hsieh and Wang 2013). Also, lucidone downregulates the expression levels of genes involved in lipogenesis including *LXR-α*, *LPL*, *aP2*, *adiponectin*, and *GLUT4* (Hsieh and Wang 2013). The dietary intake of lucidone significantly reduced high-fat-diet-induced body weight gain and epididymal and perirenal fat accumulation presumably resulting from a reduction in adipocyte diameter. Mice fed a HF diet with lucidone improved hyperglycemia, hyperinsulinemia, dyslipidemia, and hepatomegaly without kidney lesion (Hsieh and Wang 2013). This study suggests that lucidone as a nutraceutical supplement prevents obesity and associated metabolic disorders (Fig. 11.5).

11.3.4 Dermatoprotective Effect

In humans, the skin is the largest organ of the integumentary system. It protects the body from microbes and noxious substances (toxic chemicals and ultraviolet radiation), which result in skin aging, inflammation, and cancer. Several phytochemicals have been reported as potent skin-protecting agents. For example, sauchinone, a lignan from *Saururus chinensis*, protects human skin keratinocytes against ultraviolet B-induced photoaging by regulating HO-1-mediated antioxidant defense mechanism. Sauchinone also inhibits UVB-induced matrix metalloproteinase-1 (MMP-1) and reduction in type-1 collagen in skin keratinocytes (Park et al. 2013). A recent study showed that lucidone protects human skin keratinocytes (HaCaT cells) from free radical inducer 2,2′-Azobis(2-amidinopropane) dihydrochloride (AAPH)-induced oxidative damage and inflammation. Lucidone pretreatment

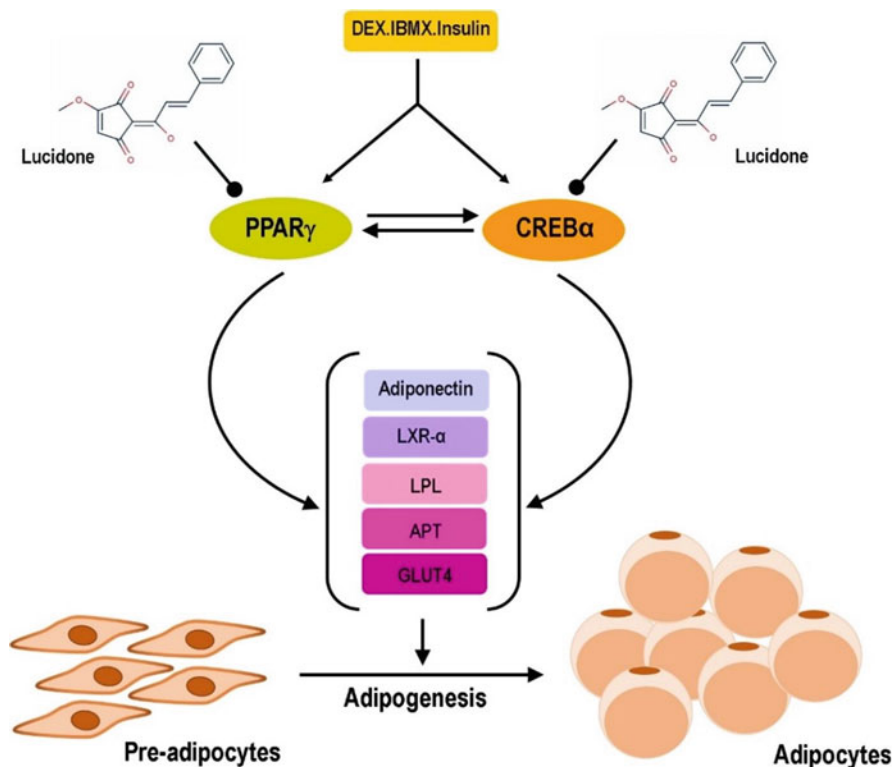

Fig. 11.5 Schematic representation of hypolipidemic effects of lucidone (3T3-L1 preadipocytes were stimulated with a mixture of 1 μM dexamethasone (DEX), 0.52 mM isobutylmethylxanthine (IBMX), and 0.17 μM insulin for 2 days)

(0.5–10 μg/mL) markedly increased HaCaT cell viability and inhibited AAPH-induced intracellular ROS generation, lipid peroxidation, and DNA damage (Kumar et al. 2013). The protective and preventive mechanisms of lucidone are mediated by the induction of an antioxidant gene HO-1 gene through the transcriptional activation of Nrf2 (Fig. 11.4). The study also reported that pretreatment with lucidone significantly inhibited AAPH-induced inflammatory chemokine prostaglandin E_2 (PGE_2) production and the expression of cyclooxygenase-2 (COX-2) in HaCaT cells. Additionally, lucidone protects human keratinocytes against AAPH-induced inflammation through the suppression of NF-κB and MAPKs signaling pathways. Another study revealed that pretreatment with lucidone (1–4 μM) significantly protected keratinocytes from UVA (15 J/cm^2)-induced cell death, excessive ROS generation, LDH release, lipid peroxidation, and DNA damage (Deng et al. 2011). In addition, lucidone inhibited the UVA-induced apoptosis of HaCaT cells (Deng et al. 2011). The antioxidant potential of lucidone was directly correlated with the induction of antioxidant genes, including HO-1, NQO-1, and γ-GCLC by transcriptional

activation of Nrf2, which was confirmed by the fact that in Nrf2 knockdown cells lucidone failed to protect UVA-induced oxidative stress or cell death (Deng et al. 2011). These findings suggest that lucidone is capable of protecting skin cells from UVA-irradiated damage (Fig. 11.4).

11.3.5 The Skin-Whitening Effect

The most common factor triggering skin pigmentation is ultraviolet (UV) radiation, which increases the production of ROS and pro-inflammatory cytokines and secretion of a α-melanocyte-stimulating hormone (α-MSH). It is well known that α-MSH plays a functional role in melanin biosynthesis. Melanin synthesis takes place in the specialized cells known as melanocytes, where α-MSH binds with melanocortin 1 receptor (MC1R) and regulates the intracellular cyclic adenosine monophosphate (cAMP), which is involved in the microphthalmia-associated transcription factor (MITF) gene expression. MITF, a basic leucine zipper transcription factor, is required for the transcription of tyrosinase, tyrosinase-related protein-1 (TRP-1), and dopachrome tautomerase (Dct) genes that encode enzymes implicated in melanin biosynthesis (Chang 2012). The synthesized melanin converts into melanosomes in melanocytes and moves to neighboring keratinocytes (Marks and Seabra 2001). Hyperpigmentation has psychosocial and cosmetic relevance; therefore, considerable efforts have gone into to the screening of effective depigmenting agents.

Tyrosinase is a multifunctional copper-containing enzyme widely distributed in plants and animals. It plays a key role in melanin biosynthesis. Tyrosinase is majorly involved in the first two steps of melanin biosynthesis pathway: hydroxylation of monophenol to o-diphenol (monophenolase or cresolase activity) and oxidation of diphenol to o-quinones (diphenolase or catecholase activity). These both steps use molecular oxygen followed by a series of nonenzymatic steps. Therefore, tyrosinase inhibitors can be clinically useful for the treatment of some dermatological disorders associated with hyperpigmentation. Many researchers are working on to isolate tyrosinase inhibitors from natural sources such as arbutin, kojic acid, gallic acid, ascorbic acid, and hydroquinones (Kim and Uyama 2005) (Fig. 11.6).

A previous study by Kang et al. (2008) reported that EtOH extracts and subfractions of leaves of *Lindera erythrocarpa* exerted antioxidant and anti-melanogenic effects in vitro. The tyrosinase inhibitory effect of ethanol extract was higher than hexane fraction. In contrast, CH_2Cl_2 fraction showed a higher inhibitory effect on α-MSH-stimulated melanin biosynthesis in melanoma B16F10 cell. Bioactive fraction-guided investigations led to the isolation of two compounds, lucidone and methyl linderone, as characterized by spectroscopic techniques including 1D, 2D NMR, and HR-MS. Lucidone and methyl linderone compounds were acting as a potent tyrosinase inhibitors compared to positive control (arbutin). These results suggest that extract of *Lindera erythrocarpa* could be used as a functional biomaterial in developing a skin-whitening agent having the antioxidant activity (Lin et al. 2007). However, this study barely explained the molecular mechanism involved in

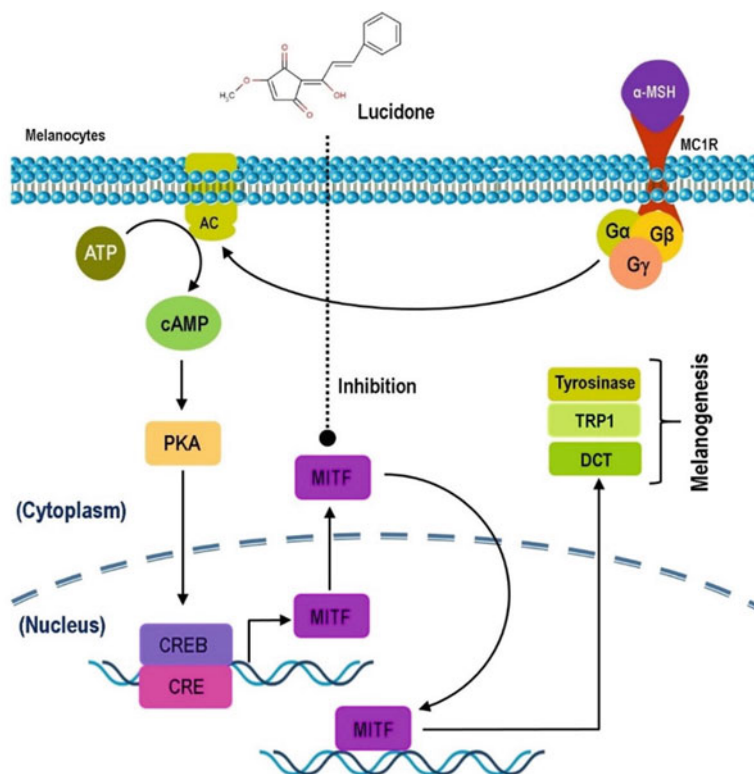

Fig. 11.6 Schematic representation of the anti-melanogenic effect of lucidone

the anti-melanogenic effects. After 2 years, we found that lucidone, isolated from the fruits of *Lindera erythrocarpa*, strongly inhibits mushroom tyrosinase activity (Kumar et al. 2010). The effects of lucidone on tyrosinase were further examined in α-MSH-induced B16 melanoma cells. Lucidone significantly inhibited tyrosinase activity and led to decreased melanin content in cultured B16 melanoma cells. Further molecular analysis showed that lucidone significantly attenuates the expression of tyrosinase and MITF proteins in a dose-dependent manner (Kumar et al. 2010). The reduction in tyrosinase protein expression by lucidone is extended to its transcriptional levels as lucidone significantly inhibited α-MSH-induced tyrosinase mRNA expression (Kumar et al. 2010). A previous report indicates that α-MSH-induced MITF activation is negatively regulated by ERK1/2 (Chang 2012). However, according to our results, lucidone did not play a major role in the induction of ERK activation. It is likely that the hydroxyl group in lucidone plays a key role in the direct tyrosinase inhibition. Most of the tyrosinase inhibitors are polyphenol derivatives such as flavonoids, resveratrol, 3,5-dihydroxyphenyl decanoate, and 5-(hydroxymethyl)-2-furfural that are rich in hydroxyl and methoxy groups. Our

results also indicated that the anti-melanogenic activity of lucidone is probably due to its downregulation of tyrosinase gene through the transcriptional suppression of MITF. Thus, lucidone has potential as a cosmeceutical agent for the hyperpigmented skin disorders.

11.3.6 Structure-Activity Relationship

Structure-activity relationship (SAR) is a means by which the effect of a drug or toxic chemical on an animal, plant, or the environment can be related to its molecular structure. The analysis of SAR enables the determination of the chemical groups responsible for evoking a target biological effect in the organism. It allows modifying the effect or the potency of a bioactive compound by changing its chemical structure. Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compounds and test the modifications for their biological effects. The basic assumption for all molecule-based hypotheses is that similar molecules have similar activities. This principle is the basis of SAR. However, the underlying problem is how to define a small difference on a molecular level, since each kind of activity, e.g., reaction ability, biotransformation ability, solubility, target activity, and so on, may depend on another difference (Patani and LaVoie 1996). Nevertheless, in general, one is more interested in finding strong trends. Created hypotheses usually rely on a finite number of chemical data. Thus, the induction principle should be respected to avoid over fitted hypotheses and driving over fitted and useless interpretations on structural/molecular data.

α,β-Unsaturated ketones have displayed diverse biological activities such as antimicrobial, antitumor, and plant growth regulation (Altalbawy 2013). The structure-activity relationship of these compounds has pointed out that the biological activity is attributed to the presence of α,β-unsaturated carbonyl group (Bag et al. 2013). Structurally, α,β-unsaturated ketones can be considered as a Michael acceptor, an active moiety often employed in the design of enzyme inhibitors.

Surh et al. (2000) studied anti-inflammatory activity of curcumin in TPA-induced mice dorsal skin. Curcumin potentially suppressed NF-κB and AP-1 activity (Surh et al. 2000). It is already known that curcumin has two α,β-unsaturated ketone moieties (Fig. 11.7). Thus, this compound may covalently interact with nucleophilic sites of the above transcription factors through Michael addition, thereby hampering DNA binding capability. Surh et al. also demonstrated the antioxidant-mediated hepatoprotective efficacy of curcumin (Surh et al. 2000). He proposed that curcumin has α,β-unsaturated ketone moiety and can, therefore, act as Michael reaction acceptors that can modify cysteine thiols located in Keap1 protein.

A previous study has shown that lucidone is chemically architectured with a cyclopentenedione ring, enol hydroxyl functionality, and styryl moiety (Ng et al.

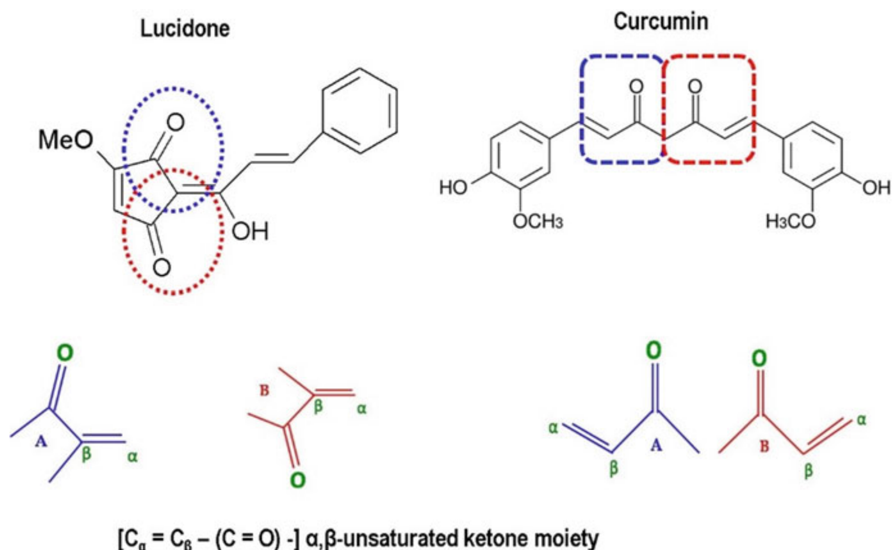

Fig. 11.7 A comparative structure-activity relationship of lucidone and curcumin

1990). The cyclopentenedione ring is made up of two α,β-unsaturated ketone moiety functional components (Fig. 11.7). We hypothesized that lucidone might have anti-inflammatory and hepatoprotective effects. Thereby, in our study, we designed to evaluate the anti-inflammatory and hepatoprotective activity of lucidone compared with curcumin.

11.4 Conclusion and Future Perspectives

Over the past five decades, changes in lifestyle patterns including diet and physical activity and the incidences of chronic and metabolic diseases such as liver diseases, lung diseases, cardiovascular diseases, diabetes, and certain types of cancers are increasing worldwide and hence are a public health concern with major economic impacts. However, the pathogenesis of these diseases is different and regulated by one or more molecular candidates that are commonly up- or downregulated leading to the notion that these could be common molecular targets in the prevention or therapeutic interventions of diseases. Since human civilization, ethnomedicine in the form of herbs and food has been contributing to disease prevention and therapy; however, rigorous experimental-based evidence in support of ethnomedicine-derived notions would lead to products relevant to the drug development. Several phytocompounds such as those in edible plants or spices are known to target multiple molecular signaling pathways, thus providing a promising preventive or

therapeutic potential against several diseases. For example, resveratrol from grapes (Pirola and Frojdo 2008), curcumin from turmeric (Lin 2007), epigallocatechin gallate from green tea (Pan et al. 2011), and schisandrin B from *Schisandra chinensis* (Fructus Schisandrae) (Hong et al. 2015) have been reported to regulate multiple molecular targets. These natural compounds have also been tested in preclinical and clinical trials as potential therapeutic agents against several diseases. In this context, lucidone is an emerging natural compound of interest with similar potency as curcumin, resveratrol, and EGCG. In the above subsections, we have discussed in detail the health-promoting effects of lucidone. These effects can be broadly divided according to the regulation of differential molecular targets. First, there is an increasing body of evidence suggesting the use of lucidone in the treatment of inflammatory disorders. The anti-inflammatory effects of lucidone rendered through the inhibition of pro-inflammatory molecules (NO, PGE_2, and TNF-α) and their mediators (iNOS, COX-2, and TNF-α) via downregulation of NF-κB/MAPKs signaling pathways. Second, the role of lucidone on liver protection is elucidated by inhibition of ROS generation by induction of internal antioxidant genes such as HO-1 and NQO-1 through the upregulation of Nrf2 signaling cascades. Beneficial health effects of lucidone are further extended to its potential role to treat other ailments such hepatitis C infections as well as liver diseases through the induction of Nrf2-mediated antioxidant defense mechanism. Third, in vitro and in vivo experimental evidence suggests the use of lucidone in the treatment of metabolic diseases. Much of these effects rendered through lucidone's efficacy to inhibit preadipocyte differentiation in vitro and hypolipidemic effects in vivo. Lucidone inhibited 3T3-L1 adipocyte differentiation by suppressing PPARγ and C/EBPα transcription factors. Lucidone also downregulates the expression levels of *LXR-α*, *LPL*, *aP2*, *adiponectin*, and *GLUT4* in vitro. A dietary intake of lucidone significantly reduced high-fat-diet-induced body weight gain and epididymal and perirenal fat accumulation presumably resulting from a reduction in adipocyte diameter. Mice fed an HF diet with lucidone improved hyperglycemia, hyperinsulinemia, dyslipidemia, and hepatomegaly without kidney lesion. Fourth, lucidone treatment protects skin keratinocytes from free radical-induced oxidative damage and inflammation and UVA-induced apoptotic cell death in vitro. The molecular mechanisms involved in the induction of antioxidant genes HO-1, NQO-1, and γ-GCLC through the transcriptional activation of Nrf2. In addition, lucidone inhibits free radical-induced inflammation in keratinocytes by inhibiting pro-inflammatory chemokine PGE_2 and its corresponding mediator COX-2 through the transcriptional suppression of NF-κB/MAPKs. Lucidone treatment provokes α-MSH-induced hyperpigmentation in melanocytes through the inhibition of tyrosinase enzymes and their transcription factor MITF. Moreover, cell-free analysis confirms that lucidone can inhibit tyrosinase enzyme activity directly. However, there is little information on the bioavailability, pharmacokinetics, and pharmacodynamics of lucidone about its beneficial health effects. The scientific knowledge in this area is limited, and hence extensive preclinical and clinical research needs to be carried out before advocating the safe and efficacious use of lucidone and lucidone-rich plant extracts against the prevention and control of diseases. Furthermore, such research may assist in the

development of evidence-based regulation of lucidone and lucidone-containing products as they become increasingly popular and enter the market.

References

Altalbawy FMA (2013) Synthesis and antimicrobial evaluation of some novel bis-α, β-unsaturated ketones, nicotinonitrile, 1,2-dihydropyridine-3-carbonitrile, fused thieno[2,3-b]pyridine and pyrazolo[3,4-b]pyridine derivatives. Int J Mol Sci 14(2):2967–2979. doi:10.1139/v02-194

Antkowiak R, Antkowiak WZ, Banczyk I et al (2003) A new phenolic metabolite, involutone, isolated from the mushroom *Paxillus involutus*. Can J Chem 81(1):118–124. doi:10.1139/v02-194

Babu KS, Li XC, Jacob MR et al (2006) Synthesis, antifungal activity, and structure-activity relationships of coruscanone A analogues. J Med Chem 49(26):7877–7886. doi:10.1021/jm061123i

Bag S, Ghosh S, Tulsan R et al (2013) Design, synthesis and biological activity of multifunctional α, β- unsaturated carbonyl scaffolds for Alzheimer's disease. Bioorg Med Chem Lett 23(9):2614–2618. doi:10.1016/j.bmcl.2013.02.103

Bao W, Li K, Rong S et al (2010) Curcumin alleviates ethanol-induced hepatocytes oxidative damage involving heme oxygenase-1 induction. J Ethnopharmacol 128(2):549–553. doi:10.1016/j.jep.2010.01.029

Braudeau C, Bouchet D, Toquet C et al (2003) Generation of heme oxygenase-1-transgenic rats. Exp Biol Med (Maywood) 228(5):466–471

Chang TS (2012) Natural melanogenesis inhibitors acting through the down-regulation of tyrosinase activity. Materials 5(9):1661

Chen WC, Wang SY, Chiu CC et al (2013) Lucidone suppresses hepatitis C virus replication by Nrf2-mediated heme oxygenase-1 induction. Antimicrob Agents Ch 57(3):1180–1191. doi:10.1128/AAC.02053-12

Chen S, Wang L, Zhang W et al (2015) Secondary metabolites from the root of *Lindera reflexa* Hemsl. Fitoterapia 105:222–227. doi:10.1016/j.fitote.2015.07.005

Comai S, Dall'Acqua S, Grillo A et al (2010) Essential oil of *Lindera neesiana* fruit: chemical analysis and its potential use in topical applications. Fitoterapia 81(1):11–16. doi:10.1016/j.fitote.2009.06.017

Davis RL, Dertien J, Syapin PJ (2002) Ethanol-induced modulation of inducible nitric-oxide synthase activity in human A172 astrocytoma cells. Alcohol Clin Exp Res 26(9):1404–1411. doi:10.1097/01.ALC.0000030841.92766.80

Deng XS, Deitrich RA (2007) Ethanol metabolism and effects: nitric oxide and its interaction. Curr Clin Pharmacol 2(2):145–153

Deng Z, Zhong H, Cui S et al (2011) Cytotoxic sesquiterpenoids from the fruits of *Lindera communis*. Fitoterapia 82(7):1044–1046. doi:10.1016/j.fitote.2011.06.012

Farombi EO, Shrotriya S, Na HK et al (2008) Curcumin attenuates dimethylnitrosamine-induced liver injury in rats through Nrf2-mediated induction of heme oxygenase-1. Food Chem Toxicol 46(4):1279–1287. doi:10.1016/j.fct.2007.09.095

Ferguson BS, Nam H, Morrison RF (2016) Curcumin inhibits 3T3-L1 preadipocyte proliferation by mechanisms involving post-transcriptional p27 regulation. Biochem Biophys Rep 5:16–21. doi:10.1016/j.bbrep.2015.11.014

Fernández Checa JC, Bellentani S, Tiribelli C (2002) Alcohol-induced liver disease: from molecular damage to treatment. Rev Med Chil 130:681–690

Fernandez-Checa JC, Colell A, Mari M et al (2005) Ceramide, tumor necrosis factor and alcohol-induced liver disease. Alcohol Clin Exp Res 29(11):151S–157S

Hong M, Li S, Tan HY (2015) Current status of herbal medicines in chronic liver disease therapy: the biological effects, molecular targets and future prospects. Int J Mol Sci 16(12):28705–28745. doi:10.3390/ijms161226126

Hsieh YH, Wang SY (2013) Lucidone from *Lindera erythrocarpa* Makino fruits suppresses adipogenesis in 3T3-L1 cells and attenuates obesity and consequent metabolic disorders in high-fat diet C57BL/6 mice. Phytomedicine 20(5):394–400. doi:10.1016/j.phymed.2012.11.007

Joshi SC, Mathela CS (2012) Antioxidant and antibacterial activities of the leaf essential oil and its constituents furanodienone and curzerenone from *Lindera pulcherrima* (Nees.) Benth. ex Hook. f. Phcog Res 4(2):80–84. doi:10.4103/0974-8490.94721

Kang MC, Ko RK, Lee JY, et al (2008) Antioxidant activity and whitening effect of *Lindera erythrocarpa* extract. www.earticle.net/article.aspx?sn=99232

Kim YJ, Uyama H (2005) Tyrosinase inhibitors from natural and synthetic sources: structure, inhibition mechanism and perspective for the future. Cell Mol Life Sci 62(15):1707–1723. doi:10.1007/s00018-005-5054-y

Kumar KJS, Yang JC, Chu FH et al (2010) Lucidone, a novel melanin inhibitor from the fruit of *Lindera erythrocarpa* Makino. Phytother Res 24(8):1158–1165. doi:10.1002/ptr.3018

Kumar KJS, Yang HL, Tsai YC et al (2013) Lucidone protects human skin keratinocytes against free radical-induced oxidative damage and inflammation through the up-regulation of HO-1/Nrf2 antioxidant genes and down-regulation of NF-kappaB signaling pathway. Food Chem Toxicol 59:55–66. doi:10.1016/j.fct.2013.04.055

Lee JY, Park HR, Oh YK et al (2007) Effects of transcription factor activator protein-1 on interleukin-8 expression and enteritis in response to *Clostridium difficile* toxin A. J Mol Med 85(12):1393–1404. doi:10.1007/s00109-007-0237-7

Lin JK (2007) Molecular targets of curcumin. Adv Exp Med Biol 595:227–243. doi:10.1007/978-0-387-46401-5_10

Lin CT, Chu FH, Chang ST et al (2007) Secoaggregatalactone-A from *Lindera aggregata* induces apoptosis in human hepatoma hep G2 cells. Planta Med 73(15):1548–1553. doi:10.1055/s-2007-993739

Majano PL, Medina J, Zubia I et al (2004) *N*-Acetyl-cysteine modulates inducible nitric oxide synthase gene expression in human hepatocytes. J Hepatol 40(4):632–637. doi:10.1016/j.jhep.2003.12.009

Marks MS, Seabra MC (2001) The melanosome: membrane dynamics in black and white. Nat Rev Mol Cell Biol 2(10):738–748

Moon HS, Chung CS, Lee HG et al (2007) Inhibitory effect of (-)-epigallocatechin-3-gallate on lipid accumulation of 3T3-L1 cells. Obesity 15(11):2571–2582. doi:10.1038/oby.2007.309

Ng S, Lee HH, Bennett GJ (1990) 13C NMR study on linderones and lucidones. Magn Reson Chem 28(4):337–342. doi:10.1002/mrc.1260280411

Noble M, Noble D, Fletton RA (1978) G2201-C, a new cyclopentenedione antibiotic, isolated from the fermentation broth of *Streptomyces cattleya*. J Antibiot 31(1):15–18

Oh HM, Choi SK, Lee JM et al (2005) Cyclopentenediones, inhibitors of farnesyl protein transferase and anti-tumor compounds, isolated from the fruit of *Lindera erythrocarpa* Makino. Bioorg Med Chem 13(22):6182–6187. doi:10.1016/j.bmc.2005.06.029

Pan MH, Chiou YS, Wang YJ et al (2011) Multistage carcinogenesis process as molecular targets in cancer chemoprevention by epicatechin-3-gallate. Food Funct 2(2):101–110. doi:10.1039/c0fo00174k

Pang B, Zhao LH, Zhou Q et al (2015) Application of berberine on treating type 2 diabetes mellitus. Int J Entocrinol 2015:905749. doi:10.1155/2015/905749

Park G, Kim HG, Sim Y et al (2013) Sauchinone, a lignan from *Saururus chinensis*, protects human skin keratinocytes against ultraviolet B-induced photoaging by regulating the oxidative defense system. Biol Pharm Bull 36(7):1134–1139

Patani GA, LaVoie EJ (1996) Bioisosterism: a rational approach in drug design. Chem Rev 96(8):3147–3176

Pirola L, Frojdo S (2008) Resveratrol: one molecule, many targets. IUBMB Life 60(5):323–332. doi:10.1002/iub.47

Senthil Kumar KJ, Wang SY (2009) Lucidone inhibits iNOS and COX-2 expression in LPS-induced RAW 264.7 murine macrophage cells *via* NF-kappaB and MAPKs signaling pathways. Planta Med 75(5):494–500. doi:10.1055/s-0029-1185309

Senthil Kumar KJ, Hsieh HW, Wang SY (2010) Anti-inflammatory effect of lucidone in mice *via* inhibition of NF-kappaB/MAP kinase pathway. Int Immunopharmacol 10(4):385–392. doi:10.1016/j.intimp.2009.12.013

Senthil Kumar KJ, Liao JW, Xiao JH et al (2012) Hepatoprotective effect of lucidone against alcohol-induced oxidative stress in human hepatic HepG2 cells through the up-regulation of HO-1/Nrf-2 antioxidant genes. Toxicol *in Vitro* 26(5):700–708. doi:10.1016/j.tiv.2012.03.012

Sevcikova Z, Pour M, Novak D et al (2014) Chemical properties and biological activities of cyclopentenediones: a review. Mini Rev Med Chem 14(4):322–331

Stauber RE, Stadlbauer V (2006) Novel approaches for therapy of chronic hepatitis C. J Clin Virol 36(2):87–94. doi:10.1016/j.jcv.2006.02.003

Surh YJ (2003) Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer 3(10):768–780. doi:10.1038/nrc1189

Surh YJ, Han S, Keum YS et al (2000) Inhibitory effects of curcumin and capsaicin on phorbol ester-induced activation of eukaryotic transcription factors, NF-kappaB and AP-1. Biofactors 12(1–4):107–112

Tichotova L, Matousova E, Spulak M et al (2011) Synthesis and biological activity of desmethoxy analogues of coruscanone A. Bioorg Med Chem Lett 21(20):6062–6066. doi:10.1016/j.bmcl.2011.08.059

Wang SY, Lan XY, Xiao JH et al (2008) Antiinflammatory activity of *Lindera erythrocarpa* fruits. Phytother Res 22(2):213–216. doi:10.1002/ptr.2289

Watt KD, Charlton MR (2010) Metabolic syndrome and liver transplantation: a review and guide to management. J Hepatol 53(1):199–206. doi:10.1016/j.jhep.2010.01.040

Wijeratne EM, Turbyville TJ, Zhang Z et al (2003) Cytotoxic constituents of *Aspergillus terreus* from the rhizosphere of *Opuntia versicolor* of the Sonoran Desert. J Nat Prod 66(12):1567–1573. doi:10.1021/np030266u

Wu L, Xiao F, Hu X (2013) Concise synthesis of lucidone and methyl lucidone. Chin J Org Chem 33(7):1587

Yang CP, Huang GJ, Huang HC et al (2013) The effect of the aerial part of *Lindera akoensis* on lipopolysaccharides (LPS)-induced nitric oxide production in RAW264.7 cells. Int J Mol Sci 14(5):9168–9181. doi:10.3390/ijms14059168

Yao P, Nussler A, Liu L et al (2007) Quercetin protects human hepatocytes from ethanol-derived oxidative stress by inducing heme oxygenase-1 *via* the MAPK/Nrf2 pathways. J Hepatol 47(2):253–261. doi:10.1016/j.jhep.2007.02.008

Zelik P, Lukesova A, Cejka J et al (2010) Nostotrebin 6, a bis(cyclopentenedione) with cholinesterase inhibitory activity isolated from Nostoc sp. str. Lukesova 27/97. J Enzym Inhib Med Chem 25(3):414–420. doi:10.3109/14756360903213481

Zhao Q, Zhao Y, Wang K (2006) Antinociceptive and free radical scavenging activities of alkaloids isolated from *Lindera angustifolia* Chen. J Ethnopharmacol 106(3):408–413. doi:10.1016/j.jep.2006.01.019

Zhao YY, Xiao M, Zhang CL et al (2015) Associations between the tumor necrosis factor-alpha gene and interleukin-10 gene polymorphisms and risk of alcoholic liver disease: a meta-analysis. Clin Res Hepatol Gastroenterol. doi:10.1016/j.clinre.2015.10.007