Chapter 15
Evidence-based Materia Medica for Cancer Chemoprevention

Sunil Prabhu, Ying Huang, and Jeffrey Wang

Abstract Cancer is the second leading cause of death in the world, and current therapeutic outcomes are still not satisfactory. Cancer chemoprevention is an important strategy to reduce cancer morbidity by using non- or low-toxic natural or synthetic commodities to prevent and/or reverse the processes of neoplastic initiation and subsequent cancer development. Substantial evidence from human, animal and cell line studies has demonstrated that many herbal products used in traditional Chinese medicine (TCM) and Ayurveda medicine or traditional Indian medicine (TIM) can exert cancer chemopreventive effects. The underlying theories or philosophies for TCM and TIM to prevent cancer are very similar. The common central theme is to bring the patient back to a healthy state by modifying multiple abnormalities in the patient's body in a holistic manner. Since carcinogenesis involves multiple abnormal gene expressions and signal transduction pathways, using TCM and TIM in cancer chemoprevention may not only be possible, but can be superior to agents aiming at single molecular target. However, before TCM and TIM can be accepted widely as complementary and alternative medicines for cancer prevention, it is crucial to evaluate their clinical efficacy and understand the molecular basis of their effects based on scientific evidence. This chapter highlights major molecular mechanisms in chemoprevention and summarizes the research on ten promising cancer preventive herbal products, including nine from TCM (Danshen, Danggui, Qianghuo, Huangqin, Zicao, Dasuan, Lingzhi, Yunzhi, and Xianggu) and five from TIM (Triphala, Turmeric, Neem, Guggulu, and Sapthaparna). The challenges in developing high quality TCM and TIM cancer preventive products are discussed and an integrated strategy is proposed to facilitate the process.

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W.C.S. Cho (ed.), *Materia Medica for Various Cancers*, Evidence-based Anticancer Complementary and Alternative Medicine 2,
DOI 10.1007/978-94-007-1983-5_15,

15.1 Introduction

Cancer is the second leading cause of death after cardiovascular diseases and accounts for one quarter of all deaths in the US (Jemal et al. 2010). Overall, cancer causes more deaths than AIDS, tuberculosis, malaria and diabetes combined. In 2010, it was estimated that approximately 1.5 million people would be diagnosed with cancer and more than half million would die of this disease. By rate of occurrence, cancers of the prostate, lung and bronchus and colon and rectum among men and breast, lung and bronchus and colon and rectum among women are the three most common cancers. However, lung and bronchus cancer has the highest mortality rate in both men and women, followed by prostate cancer and breast cancer, respectively (Jemal et al. 2010).

Conventional treatment approaches for cancer are surgery, chemotherapy and radiotherapy, either alone or in combination. Additional treatment options also exist, including immunotherapy, molecular targeted therapy and hormonal therapy. Despite advances in science and technology, satisfactory therapeutic outcomes are still limited with an age-standardized death rate of 186.9 per 100,000 in the US population (Jemal et al. 2010).

Chemoprevention, using non- or low-toxic natural or synthetic substances to decrease the risk of developing cancer, has become an important approach to decrease cancer morbidity (Rao and Reddy 2004). The transformation of normal cells into cancer cells is a multi-step process that involves multiple genetic and epigenetic alterations resulting in disruption of various molecular and cellular processes (Hawk et al. 2004). In this series of events, chemoprevention can be achieved by the arrest or reversal of any or all of these processes. Mounting *in vitro* and *in vivo* studies have identified effective chemopreventive agents and molecular mechanisms in preventing cancer initiation and development (Hawk et al. 2004).

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), selenium, calcium, folic acid, and natural products derived from fruits and vegetables have been extensively studied for their cancer chemopreventive effects. However, many of these agents have not been widely adopted due to low efficacy and intolerable adverse effects such as gastrointestinal bleeding (Cuzick et al. 2009; Rothwell et al. 2010). Thus, there is an urgent need to identify non- and low-toxic preventive agents that have broad applications.

As civilization flourished, many ethnic groups developed traditional medicines to serve health need of the population. For example, traditional Chinese medicine (TCM) has been in practice for several thousand years and is still been used as an alternative and complementary medicine, with the co-existence of Western medicine in China and many Chinese-speaking communities elsewhere. The underlying theory for TCM to treat or prevent diseases is to bring the patient back to a healthy state by modifying multiple disease-causing events (Parekh et al. 2009). This is achieved by multiple components in an herb or a formula which usually contains several herbs. Since multiple genes/pathways contribute to cancer development, using TCM in cancer prevention may be superior to agents targeting a single molecular target alone (Wang et al. 2010). Thus, TCM provides an attractive resource for cancer prevention.

Similarly, Ayurveda medicine or traditional Indian medicine (TIM), much like TCM, focuses on the patient rather than the disease. Such a traditional system of medicine fundamentally aims to promote health and enhance the quality of life (QoL) with strategies for treatment of specific diseases or symptoms in a holistic fashion. In the TIM, dry powder or crude extracts of plants are used to treat various disorders including cancer. The effect of these dry powders is credited to the mixture of components in the crude extract rather than any one single compound. The rationale for this type of treatment is that the toxicity of an active component may be counteracted by another component which may not have the desired therapeutic property but instead have the ability to counteract deleterious side effects of a pure compound (Lad 2005). Although several TIM drugs have been claimed to prevent or treat different forms of cancer since ancient times, it is only recently that scientific research is revealing the true potential of these herbal medications.

It is a scientific consensus that before TIM and TCM can be accepted globally as complementary and alternative medicine for cancer prevention, it is crucial to understand the molecular basis for their cancer preventive effects. Relevant studies towards this goal have been scattered in the literature and often hard to access by newcomers interested in this type of research. This chapter summarizes the evidence-based preclinical and clinical efficacy and highlights several known molecular mechanisms for selected TIM and TCM in chemoprevention based on extensive review of English, Chinese and Indian literatures.

15.2 Molecular Targets for Cancer Chemoprevention

15.2.1 Inhibition of Cyclooxygenase-2 (COX-2)

COX enzymes (COX-1 and COX-2) catalyze the conversion of arachidonic acid to prostaglandins including PGE2 (Hung 2008). Prostaglandins have several cancer promoting properties: (a) they are growth promoters that may contribute to the proliferation of tumor cells; (b) they may act as anti-apoptotic molecules; and (c) they may suppress the antitumor activity of natural killer (NK) cells and macrophages.

COX-1 and COX-2 have distinct tissue distribution and physiologic functions in mammalian cells. COX-1 is expressed in many normal tissues and plays an important role in the maintenance of homeostasis, whereas COX-2 is an inducible enzyme activated in response to extracellular stimulations such as growth factors and proinflammatory cytokines (Simmons et al. 2004). Overexpression of COX-2 is found in cancers of colon, lung, breast and pancreas. In addition, COX-2 has been shown to stimulate the production of various angiogenic factors. For example, overexpression of COX-2 increases the production of vascular endothelial growth factor (VEGF) and promotes angiogenesis (Gately and Li 2004).

Aspirin and other NSAIDs exert their cancer chemopreventive effects mainly *via* the inhibition of COX enzymes, especially COX-2 (Cuzick et al. 2009).

15.2.2 Down-regulation of NF-κB Pathway

NF-κB is a family of transcription factors important for regulation of immune and inflammatory responses as well as cancer development and progress (Karin 2006). The activation of NF-κB leads to induced target genes that affect most of the processes that contribute to cancer development, including uncontrolled growth, invasion and metastasis. Target genes of the pathway include caspase inhibitors c-IAP1, c-IAP2, X-IAP, as well as tumor necrosis factor receptor associated factors TRAF1 and TRAF2 (Wang et al. 1998). Caspase proteins of the caspase cascade are a group of proteins essential for apoptosis or programmed cell death and thus inhibition of caspase activity by NF-κB target genes leads to non-apoptosis and tumor proliferation.

All NF-κB proteins share a Rel homology domain at the N-terminus which is responsible for DNA binding and association with its inhibitory subunits IκBs (Ghosh et al. 1998). In normal resting cells, Rel/NF-κB dimmers are sequestered to the IκBs in cytoplasm and remain inactive. Stimulation of the cell triggering signal transduction pathways ultimately leads to the activation of the IκB kinases (IKKs) which phosphorylate the IκBs and subsequently tag them for polyubiquitination and degradation by proteasomes (Ben-Neriah 2002). Proteasomal degradation of IκBs frees the NF-κB and results in accumulation of this transcription factor in the nucleus to activate genes that confer resistance to apoptotic signals. Because failure of apoptosis is one of the main causes of tumor development, inhibition of the NF-κB pathway is a useful tool in chemoprevention.

NF-κB plays multiple roles in immune and inflammatory responses and thus down-regulation of NF-κB activity also leads to other cancer preventive mechanisms (Chabot-Fletcher 1997). Suppression of NF-κB can inhibit the expression of TNF-α. Abnormal up-regulation of both COX-2 and inducible nitric oxide synthase (iNOS) have been associated with the pathophysiology of certain types of cancers and inflammatory disorders (Surh et al. 2001). iNOS is an enzyme that mediates inflammation by producing nitric oxide (NO), a pro-inflammatory mediator. The *COX-2* gene contains two NF-κB binding sites in its 5'-promoter region and is up-regulated in inflammatory response mediated by NF-κB (D'Acquisto et al. 1997). Therefore, inhibition of NF-κB may lead to suppression of COX-2 expression which in turn contributes to anti-angiogenesis and tumor suppression. Expression of iNOS is also thought to be regulated by NF-κB (Xie et al. 1994). The NF-κB pathway also up-regulates the *Bcl-2* gene which is directly linked to anti-apoptosis (Meunier and Hayashi 2010). Thus, NF-κB and its signaling pathways are attractive targets for cancer chemoprevention.

15.2.3 Activation of Intrinsic and Extrinsic Apoptotic Pathways

Some chemopreventive agents such as NSAIDs have been found to induce apoptosis through intrinsic pathways such as cytochrome c release from mitochondria and activation of caspase-9 and extrinsic pathways such as activation of caspase-8.

Release of cytochrome c leads to the formation of apoptosome complex activating caspase-9 and -3, thereby inducing apoptosis (Jana 2008).

15.2.4 Inhibition of Cell Cycle Progression

Cyclins activate cyclin-dependent kinases to promote cell growth, and their over expression has been associated with tumor development (Yang et al. 2004). Some chemopreventive agents are thought to inhibit the expression and activity of cyclins such as cyclin D1, A, B, as well as cyclin E/cyclin-dependent kinase 2 and cyclin B1/cyclin-dependent kinase. The cyclin D1 and E can be degraded by ubiquitin proteasome pathway (Boyle et al. 1999). Promoting proteasomal degradation of cyclins, which results in cell cycle arrest at the G1 phase, was proposed as a mechanism of cancer prevention by all-*trans*-retinoic acid (Dragnev et al. 2007).

15.2.5 Induction of Stress Response

Some chemopreventive agents have been found to induce endoplasmic and oxidative stress which could initiate apoptotic signals. Endoplasmic stress response can be induced due to the accumulation of unfolded proteins causing the activation of caspase-12, which further activates caspase-9 and -3, thereby inducing apoptosis (Kaufman 2002).

15.2.6 Activation of the Nuclear Factor Erythroid 2-related Factor 2 (Nrf2)-antioxidant Signaling

Environmental carcinogens are often first metabolically activated *via* Phase I enzymes (e.g. cytochrome P450). The Phase II enzymes such as NAD(P)H:quinone oxidoreductase (NQO1), heme oxygenase-1 (HO-1), gamma-glutamylcysteine synthetase (γ-GCS), and glutathione S-transferases (GSTs) facilitate the elimination of the activated carcinogens through conjugation reactions including sulfation, acetylation, and glutathione (GSH) conjugation (Kwak et al. 2004). A promising strategy for cancer chemoprevention involves the use of agents to induce the Phase II detoxifying and antioxidant genes. Nrf2, a bZIP transcription factor, plays a central role in the regulation of expression of Phase II genes by binding to the antioxidant response element (ARE) in their respective promoters (McMahon et al. 2001). Many anti-carcinogenic/antioxidant genes are under the transcriptional control of ARE. It is now known that Nrf2, which is normally sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1), dissociates from KEAP1 on exposure to

ARE-mediated inducers, translocates to the nucleus, complexes with other nuclear factors, and binds to ARE. Many ARE-mediated inducers including sulforaphane have been identified to be promising cancer preventive agents (Fahey and Talalay 1999).

15.2.7 Interference with Tumor Forming Microenvironment

Other than the drug targets located in origin of tumor cells, another potential targets for chemoprevention could be generated by considering targets in tumor-associated stromal and endothelial cells (e.g. fibroblast growth factor (FGF), VEGF), as well as targets related to a systemic reservoir of circulating cells that can be recruited to carcinogenic influence by inflammatory factors (Johnson and Brown 2010; Hanahan and Weinberg 2011). Tumor microenvironment (TME) targeting can be used as prevention strategy, i.e. to block progression of preneoplastic lesions; or create cytostatic effects to tame an aggressive cancer into a benign disease; or induce tumor dormancy; or cause the regression of established tumors; or reverse therapeutic resistance. Several preclinical reports on targeting of non-tumor cells in the TME

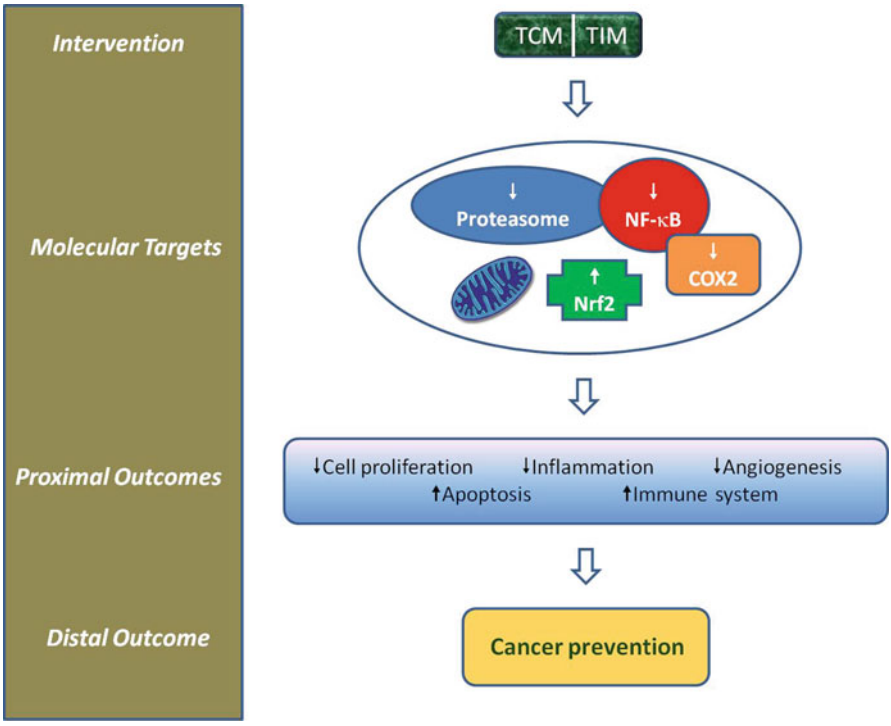


Fig. 15.1 The intervention of traditional Chinese medicine (TCM) and traditional Indian medicine (TIM) and their representative molecular targets, several proximal outcomes and eventual cancer prevention as the distal intervention outcome

showed that such an approach is feasible and that it may be beneficial to tumor bearers in the clinical setting as a neoadjuvant (Mohla and Witz 2010). However, the tumor microenvironment is complicated, which involves a multitude of candidate microenvironmental factors. Thus, targeting single molecules is not sufficient. There is great potential for multi-targeted approaches that may be more effective than single agents and also less prone to resistance. This again provides an opportunity for traditional medicine. Although this field is still in its infancy, with the advancement in understanding of the molecular properties of TME and new model systems to study TME, novel natural products may provide rich resource of drug candidates to targeting both tumor and tumor associated TME. This will expand the dimensions of targeted prevention and enhance the overall opportunity to eliminate precancer or cells at risk of eventually transitioning to invasive cancer (Mohla and Witz 2010).

A scheme depicting the intervention of TCM and TIM and their representative molecular targets, several proximal outcomes and eventual cancer prevention as the distal intervention outcome is presented in Fig. 15.1.

15.3 TCM as Cancer Chemopreventive Agents

15.3.1 Danshen

Danshen (Fig. 15.2) is the root of the plant *Salvia miltiorrhiza*, and is a widely used TCM for the treatment of cardiovascular disorders by improving blood circulation (Cheng 2006). Its major chemical constituents have been found to be lipophilic tanshinones, mainly tanshinone IIA and the hydrophilic compounds danshensu (also known as salvianolic acid A) and salvianolic acid B (Table 15.1) (Zhou et al. 2005). Recent studies have also shown that Danshen and its constituents possess anti-inflammatory effects through the inhibition of iNOS expression and cytokine secretion (Fan et al. 2009; Park et al. 2009). Tanshinone IIA has been identified with the most potent antioxidant activity and cytotoxic properties by inducing apoptosis and differentiation in various human cancer cell lines including human leukemia THP-1, breast and colon adenocarcinoma cells (Wu et al. 1991; Mosaddik 2003; Tang et al. 2003; Wang et al. 2005b; Su et al. 2008).

Tanshinone IIA also displays antioxidant protection against reactive oxygen species (ROS) induced oxidative stress through stress-activated kinases JNKs and p38 MAPK and by an increase in scavenging of ROS (Fu et al. 2007; Yang et al. 2008). The Nrf2 pathway has been known to interact with JNKs and p38 MAPK kinases which indirectly regulate the Nrf2 pathway through phosphorylation of Nrf2 (Yuan et al. 2006; Sun et al. 2009). Zhang et al. showed that Nrf2 is involved in the effects of tanshinone IIA by reversing TNF-α induced down-regulation of GSH, NADPH, and glucose 6-phosphate dehydrogenase (G6PDH) (Zhang and Wang 2007). siRNA silencing of Nrf2 abolished tanshinone IIA-induced up-regulation of GSH and

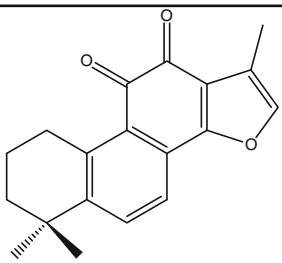
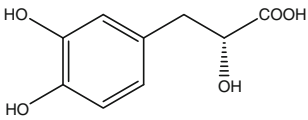
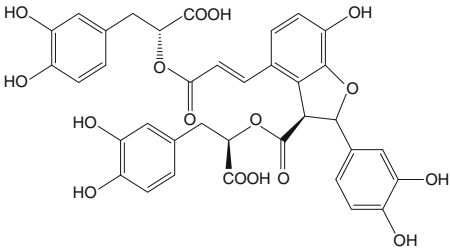
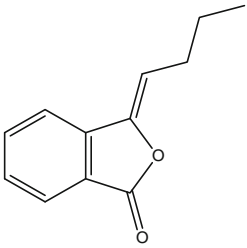
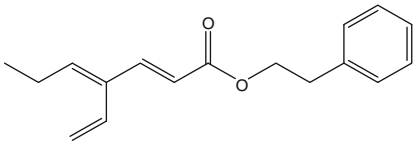
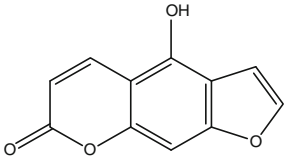
Fig. 15.2 Representative cancer chemopreventive herbs from traditional Chinese medicine

G6PDH. It has also been found that the anti-inflammatory effects of tanshinone IIA directly result from the up-regulation of HO-1 through PI3K/Akt and ERK pathways induced higher levels of Nrf2 (Chen et al. 2007). Tanshinone IIA activates the Nrf2 pathway through disruption of the Nrf2-KEAP1 complex and through kinase signaling pathways such as JNKs, p38 MAPK, PI3K/Akt, and ERK to assist in the release of Nrf2. Based on promising anticancer and chemopreventive effects, tanshinone IIA serves as a candidate for further cancer chemoprevention and treatment research.

15.3.2 Danggui

The dry root of the plant *Angelica sinesis*, Danggui (Fig. 15.2), is a TCM traditionally used in the treatment of women's menopausal symptoms. Danggui has been shown to possess anti-inflammatory properties and antioxidant activities, especially when used concurrently with other herbs (Chu et al. 2009; Yang et al. 2009). It has also been found that Danggui may exert protection against neuronal oxidative stress on rat cerebral ischemia/reperfusion models (Lin et al. 2011).

Table 15.1 Active components in chemopreventive TCMs reviewed in this chapter

Compound	TCM	Plant name	Structure
Tanshinone IIA	Danshen	*Salvia miltiorrhiza*	
Danshensu (salvianolic acid A)	Danshen	*Angelica sinesis*	
Salvianolic acid B	Danshen	*Angelica sinesis*	
Z-Ligustilide	Danggui	*Angelica sinesis*	
Phenethyl ferulate	Qianghuo	*Notopterygium forbesii*	
Bergaptol	Qianghuo	*Notopterygium forbesii*	

(continued)

It has been reported that the major lipophilic constituent of Danggui, Z-ligustilide (Table 15.2), reduces oxidative stress through up-regulation of antioxidant enzymes such as NQO1 *via* the Nrf2 pathway (Dietz et al. 2008). Also, Dan gui can protect against oxidant injury through elevated glutathione synthesis whose rate-limiting

Table 15.1 (continued)

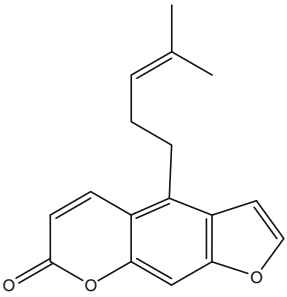
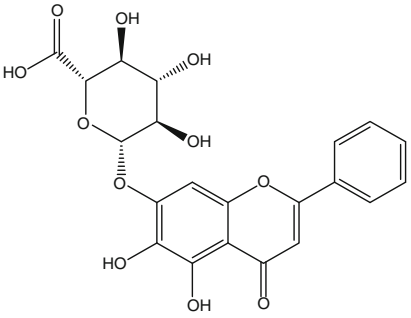
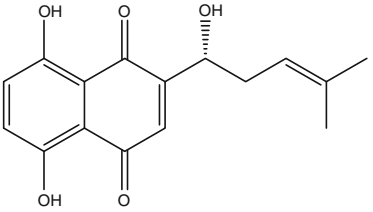
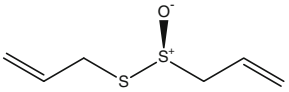
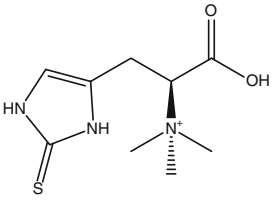
Compound	TCM	Plant name	Structure
Isoimperatorin	Qianghuo	*Notopterygium forbesii*	
Baicalin	Huangqin	*Scutellaria baicalensis*	
Shikonin	Zicao	*Lithospermum erythrorhizon*	
Allicin	Dasuan	*Allium sativum*	
Ganopoly	Lingzhi	*Ganoderma lucidum*	β-glucan polysaccharides
PSK	Yunzhi	*Coriolus versicolor*	Purified polysaccharide-K
Lentinan	Xianggu	*Lentinus edodes*	1,3 β-D-glucan (polysaccharide)
L-Ergothioneine	Xianggu	*Lentinus edodes*	

Table 15.2 Active components in chemopreventive TIMs reviewed in this chapter

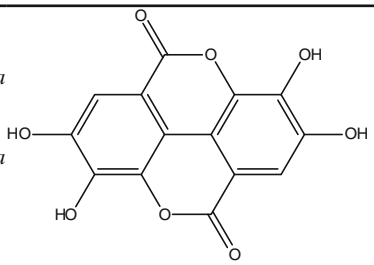
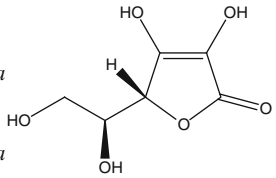
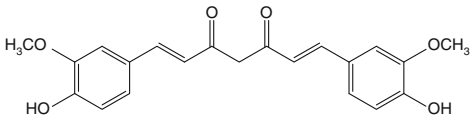
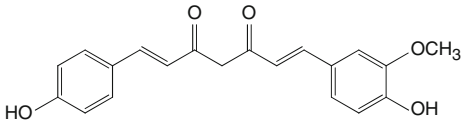
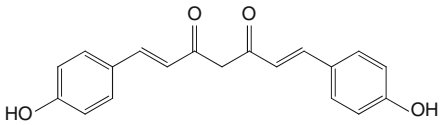
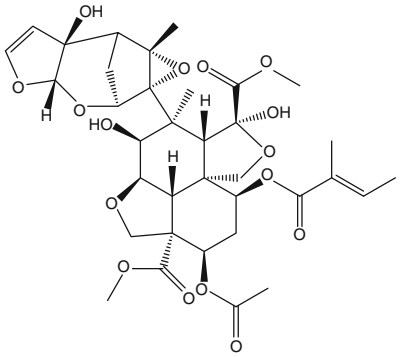
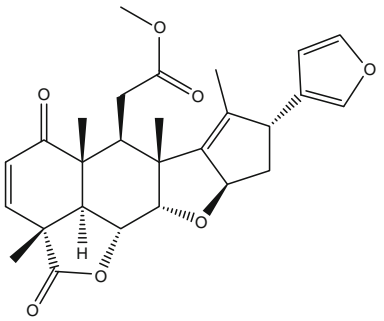
Compound	TIM	Plant name	Structure
Gallic acid	Triphala	*Emblica officinalis, Terminalia belerica and Terminalia chebula*	
Ascorbic acid	Triphala	*Emblica officinalis, Terminalia belerica and Terminalia chebula*	
Curcumin	Turmeric	*Curcuma longa*	
Demethoxy curcumin	Turmeric	*Curcuma longa*	
Bis-demethoxy curcumin	Turmeric	*Curcuma longa*	
Azadirachtin	Neem	*Azadirachta indica*	
Nimbolide	Neem	*Azadirachta indica*	

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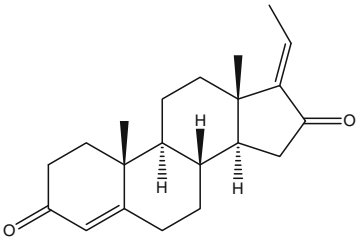
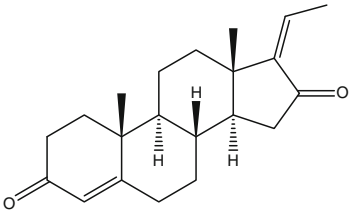
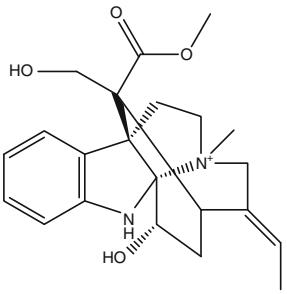
Table 15.2 (continued)

Compound	TIM	Plant name	Structure
E-Guggulsterone	Guggulu	*Commiphora mukul*	
Z-Guggulsterone	Guggulu	*Commiphora mukul*	
Echitamine	Sapthaparna	*Alstonia scholaris*	

step is regulated by the Nrf2 pathway gene γ-*GCS* (Chiu et al. 2007). The study showed that both Danggui extract and Z-lingustilide induced a dose-dependent increase of NQO1 in an ARE luciferase reporter assay. Further mass spectrometric analysis of the incubation mixture revealed that Z-lingustilide is able to alkylate cysteine residues in the KEAP1 protein which frees Nrf2 to bind to the ARE and activate transcription of *Nrf2-ARE* genes (Dietz et al. 2008). In addition, Danggui can inhibit COX-2 expression at mRNA and protein levels (Chu et al. 2009).

15.3.3 Qianghuo

Qianghuo (Fig. 15.2), prepared from the root of the plant *Notopterygium forbesii*, has been used to treat the common cold, headache, rheumatism, and may possibly possess anti-inflammatory, diaphoretic, and analgesic properties (Yang et al. 1991; Okuyama et al. 1993; Guo et al. 2001).

The mechanism for Qianghuo's cancer preventive effects was found to be correlated to the up-regulation of HO-1 and effects on oxidative stress (Tang et al. 2008, 2009). Qianghuo induced oxidative stress and a rise in HO-1 proteins in human fetal hepatocytes through the activation of the Nrf2 pathway by the p38 MAPK pathway. The active constituents were identified to be phenethyl ferulate, bergaptol, and isoimperatorin (Table 15.1) (Wang and Wang 1996). Qianghuo and its constituents also attenuate lipopolysaccharide induced pro-inflammatory responses and iNOS and COX-2 overexpression (Tang et al. 2009).

15.3.4 Huangqin

The root of *Scutellaria baicalensis*, Huangqin (Fig. 15.2), is well known for its anti-inflammatory activity and its role in the treatment of various kinds of cancers both *in vivo* and *in vitro* (Nelson and Montgomery 2003). The main active constituent of Huangqin is baicalin (Table 15.1) which can be converted into baicalein by removal of the sugar moiety in the intestines. The mechanisms of action of Huangqin including inhibition of ERK, Akt, and NF-κB activities contribute to cell cycle arrest and tumor suppression (Peng et al. 2008). Huangqin also inhibits synthesis of eicosanoid, an important inflammatory mediator and a marker for COX-2 and tumor proliferation (Pidgeon et al. 2002). Baicalin has also been found to induce apoptosis in prostate cancer cell lines through cell cycle arrest and caspase-3 activity which is also linked with NF-κB inhibition (Chan et al. 2000). Inhibition of interleukin-12 production, a factor in tumor angiogenesis and a therapeutic target for cancer, was also shown in primary mouse macrophages as well as RAW264.7 monocytic cell line by Huangqin (Kang et al. 2003).

15.3.5 Zicao

Zicao or purple grass (Fig. 15.2), the dried root of *Lithospermum erythrorhizon*, is used in TCM for anti-inflammation in such diseases as macular eruptions, measles, sore throat, carbuncles, and burns (Chen et al. 2002). Shikonin (Table 15.1) is a major naphthoquinone pigment isolated from Zicao. Recently, shikonin and its derivatives have been found to possess antitumor properties and induce apoptosis both *in vitro* and *in vivo*. It has been shown that growth inhibition and induction of apoptosis by shikonin and its derivatives are at least partly through the inactivation of NF-κB through IκB protection in human oral squamous cell carcinoma cell lines (Min et al. 2008). Shikonin inhibited tumor cell proliferation, cell cycle progression, and induced apoptosis and caspase activity. Specific inhibitory effects of shikonin on VEGF production due to NF-κB inhibition which leads to inhibition of tube formation in tumor cells have been shown in lung carcinoma bearing mice (Lee et al. 2008). The shikonin derivative DMNQ S-64 has been reported to induce

apoptosis *via* caspase activation and COX-2 inhibition in both lung cancer cells and human myeloid leukemia cells (Lim et al. 2007; Park et al. 2008). Another shikonin derivative SYUNZ-7 has been found to have antitumor effects in a time and concentration dependent manner in human nasopharyngeal cancer cell line CNE2 grafted mice *in vivo* and *in vitro* through the inhibition of angiogenesis, tumor cell apoptosis and cell cycle blocking (Huang et al. 2005).

15.3.6 Dasuan

Dasuan or garlic (Fig. 15.2) is a spice derived from the bulb or clove of the garlic plant *Allium sativum* and has been shown to be effective against a variety of diseases including hyperlipidemia, hypertension and atherosclerosis (Amagase et al. 2001). More recently, interest is building in investigating the use of garlic in the chemoprevention of cancer. Several case-controlled studies conducted in Europe have indicated an association between garlic consumption and decreased risk of common cancers (Amagase 2006). Garlic supplements can be classified into four groups: Garlic essential oil, garlic oil macerate, garlic powder, and garlic extract.

Garlic essential oil is obtained by passing steam through garlic. Commercially available garlic oil capsules generally contain vegetable oil, but only have a small amount of garlic essential oil because of its strong odor.

Garlic oil macerate products are made from encapsulated mixtures of whole garlic cloves ground into vegetable oil.

Garlic powder is produced by slicing or crushing garlic cloves, then drying and grinding them into powder. Garlic powder is used as a flavoring agent for condiments and food and is thought to retain the same ingredients as raw garlic.

Garlic extract is made from whole or sliced garlic cloves that are soaked in an alcohol solution (an extracting solution) for varying amounts of time. Powdered forms of the extract also are available.

The intact cells of garlic contain an odorless, sulfur-containing amino acid derivative known as alliin. When the cells are crushed, alliin comes into contact with the enzyme alliinase located in neighboring cells and is converted to allicin (Table 15.1). Allicin is a potent antibiotic, but it is highly odoriferous and unstable. Allicin is described as possessing anti-platelet, antibiotic, and anti-hyperlipidemic activity. Most authorities agree that the best measure of the total activity of garlic is its ability to produce allicin, which, in turn, results in the formation of other active constituents (Amagase et al. 2001). Garlic might stimulate both humoral and cellular immunity, causing T cell proliferation, restoring suppressed antibody responses (Hodge et al. 2002), and stimulating macrophage cytotoxicity on tumor cells. Garlic might increase selenium absorption with possible protection against tumorigenesis (Hirsch et al. 2000). In addition, garlic may protect against certain cancers by halting cell cycle progression and inducing apoptosis of cancer cells as well as by decreasing angiogenesis and influencing carcinogen metabolism (Herman-Antosiewicz et al. 2007).

Using data from an integrated network of Italian and Swiss case-control studies, the relation between frequency of onion and garlic use and cancer at several sites were examined (Galeone et al. 2006). The odds ratios (ORs) using multivariate logistic regression models were calculated; a uniquely large data set from southern European populations showed an inverse association between the frequency of use of allium vegetables and the risk of several common cancers.

Another study conducted meta-analyses of the epidemiologic literature on the association between garlic consumption and risk of stomach, colon, head and neck, lung, breast, and prostate cancers (Fleischauer et al. 2000). Meta-analyses were conducted for all cancers mutually and separately for colorectal and stomach cancers in relation to consumption of exclusively raw garlic, cooked garlic, or both (RC garlic). Eighteen studies reported a relative risk estimate for RC garlic consumption and cancer risk. In the meta-analyses of colorectal and stomach cancer, a high intake of RC garlic was associated with a protective effect against stomach and colorectal cancers. However, heterogeneity of effect estimates, differences in dose estimation, publication bias, and possible alternative hypotheses (e.g. confounding by total vegetable consumption) preclude sole reliance on summary effect estimates.

In addition, garlic intake was inversely associated with cancer of the prostate (Hsing et al. 2002) and endometrium (Galeone et al. 2009). Epidemiologic and laboratory studies suggest that allium vegetables and garlic constituents have antitumor effects. In a population-based, case-control study conducted in Shanghai, China, the association between intake of allium vegetables, including garlic, scallions, onions, chives, and leeks, and the risk of prostate cancer was studied (Hsing et al. 2002). In-person interviews and information collected on 122 food items from 238 case subjects with incident, histologically confirmed prostate cancer and from 471 male population control subjects. Men in the highest of three intake categories of total allium vegetables (>10.0 g/day) had a statistically significantly lower risk of prostate cancer than those in the lowest category (<2.2 g/day). Similar comparisons between categories showed reductions in risk for men in the highest intake categories for garlic and scallions. The reduced risk of prostate cancer associated with allium vegetables was independent of body size, intake of other foods, and total calorie intake and was more pronounced for men with localized than with advanced prostate cancer.

The relationship between onion and garlic intake and endometrial cancer, using data from an Italian case-control study was examined (Galeone et al. 2009). Data from a multi-center case-control study of 454 endometrial cancer cases and 908 controls, admitted to the same hospitals for a wide spectrum of acute, non-neoplastic conditions was monitored. Information was collected by trained interviewers using a validated method. Multivariate odds ratios and 95% confidence intervals were obtained after allowance for recognized confounding factors. The study found a moderate protective role of allium vegetables on the risk of endometrial cancer.

In patients with advanced cancers, aged garlic extract (AGE) improved NK cell number and activity, but not QoL (Ishikawa et al. 2006). AGE has manifold biological activities including immunomodulative and antioxidative effects. It is used as a major component of non-prescription tonics and cold-prevention medicines

or dietary supplements. Advanced-cancer patients decline in immune functions and QoL. The study's subjects were patients with inoperable colorectal, liver, or pancreatic cancer. In a randomized double-blind trial, AGE was administered to one group and a placebo was administered to another for 6 months. The primary endpoint was a QoL questionnaire based on the Functional Assessment of Cancer Therapy (FACT). The sub-endpoints were changes in the NK cell activity and the salivary cortisol level from before and after administering AGE. Although no difference was observed in QoL, both the number of NK cells and the NK cell activity increased significantly in the AGE group. No adverse effect was observed in either group. The study showed that administering AGE to patients with advanced cancer of the digestive system improved NK cell activity, but caused no improvement in QoL.

In patients with a history of adenomas, supplementation with AGE reduced both the number and size of subsequent colorectal adenomas (Tanaka et al. 2006). Epidemiological and animal studies suggest AGE and its organosulfur constituents, such as *S*-allylcysteine and *S*-allylmercapto-cysteine have anti-carcinogenic effects. To confirm these effects in humans, a preliminary double-blind, randomized clinical trial using high dose AGE (AGE 2.4 ml/day) as an active treatment and low dose AGE (AGE 0.16 ml/day) as a control was performed on patients with colorectal adenomas-precancerous lesions of the large bowel. The study enrolled 51 patients who were diagnosed as carrying colorectal adenomas. The patients were randomly assigned to the two groups after adenomas larger than 5 mm in diameter were removed by polypectomy. The number and size of adenomas right before intake (0 month) and at 6 and 12 months after intake were measured using colonoscopy. The number of adenomas increased linearly in the control group from the beginning (the baseline), but AGE significantly suppressed both the size and number of colon adenomas in patients after 12 months of high-dose treatment ($p = 0.04$). The results suggest AGE suppresses progression of colorectal adenomas in humans. It appears that AGE has multiple pathways to reduce cancer incidence and suppress its growth and proliferation.

15.3.7 Lingzhi

Many types of mushrooms are used in TCM, among which Lingzhi (Fig. 15.2) is the most precious (Sullivan et al. 2006). Lingzhi is derived from the cap and stem of the mushroom *Ganoderma lucidum* and used as an immune stimulant by patients with HIV or cancer. The active constituents are β-glucan polysaccharides (Fig. 15.2) and triterpenes (Huang 1999), which seem to have the most biological activity. The triterpenes are reported to have adaptogenic and antihypertensive, as well as anti-allergic effects. In addition, they may inhibit tumor invasion by reducing matrix metalloproteinase expression and tumor metastases by limiting attachment to endothelial cells (Li et al. 2008; Mao et al. 1999).

A recent study was designed to determine the antitumor efficacy of *Ganoderma lucidum* polysaccharides (GlPS) and the possible mechanism covering this effect (Li et al. 2008). Proteomic study revealed marked protein changes after the process of treatment. Three significantly changed proteins were identified as haptoglobin, apolipoprotein A-II and serum amyloid A (SAA), respectively. The adhesion assay showed that GlPS-treated sera dramatically inhibited the adhesion ability of human prostate carcinoma (PC-3M) cells to human umbilical cord vascular endothelial cells (HUVECs), and this effect partially recovered after immunodepletion by the antibody against SAA. Collectively, these results suggest that GlPS inhibited the tumor growth and tumor cell adhesion to HUVECs *via* up-regulation of SAA protein expression.

β-glucans have demonstrated antitumor and immuno-stimulating activities (Chan et al. 2008). They can induce the maturation of normal and leukemic monocytes into dendritic cells (Wang et al. 1997). Extracts of Lingzhi have demonstrated the ability to stimulate macrophages and to alter the levels of TNF and interleukins (Chen et al. 2004). Furthermore, Lingzhi extracts can inhibit 5α-reductase, an important enzyme that converts testosterone to dihydrotestosterone and is up-regulated in benign prostatic hyperplasia (Noguchi et al. 2008).

Studies in rats have shown that Lingzhi extracts may alleviate chemotherapy-induced nausea (Wang et al. 2005a). Chemotherapy is highly cytotoxic, causing a number of severe adverse effects such as nausea and vomiting. Herbal medicines, which can often be used on a daily basis for prolonged treatment, may be clinically beneficial. Lingzhi mushroom has been recognized as a remedy in treating a number of medical conditions, including balancing immunity and decreasing drug-induced side effects. It has been shown that rats react to emetic stimuli, like the chemotherapy agent cisplatin, by increased consumption of kaolin, known as pica; and this rat model has been utilized to evaluate novel anti-emetic compounds. In this study, the effects of a Lingzhi extract in attenuating cisplatin-induced nausea and vomiting in the rat pica model was evaluated (Wang et al. 2005a, b). Observations showed that the intraperitoneal cisplatin injection caused a significant increase in kaolin intake at 24, 48, 72, and 96 h, reflecting cisplatin's nausea and vomiting action. This cisplatin-induced kaolin intake dose-dependently decreased after 1, 3, and 10 mg/kg Lingzhi extract injection. In addition, there was a significant reduction of food intake after cisplatin. The cisplatin-induced food intake reduction improved significantly after Lingzhi extract administrations in a dose-related manner, suggesting a supportive effect of the extract on general body condition. Future controlled clinical trials are needed to evaluate the safety and effectiveness of this herbal medication.

In clinical studies, Lingzhi increased plasma antioxidant capacity and enhanced immune responses in advanced-stage cancer patients (Gao et al. 2003). Thirty-four patients with advanced-stage cancer of various tissues were given 1,800 mg of oral ganopoly (crude polysaccharide fractions extracted from Lingzhi) three times daily before meals for 12 weeks. Cytokines, T cell subsets, and NK activity were measured to assess the effects of ganopoly. Researchers found a significant increase in T cell populations and NK activity at the 12-week period compared to baseline although the mechanism is unclear.

Complete regression of high-grade lymphoma is extremely rare, but one report was made mediated by Lingzhi recently (Cheuk et al. 2007). A 47-year-old man presented with epigastric pain. Endoscopy revealed a large gastric ulcer, which on biopsy was diagnostic of large B cell lymphoma. At gastrectomy 11 days later, no evidence was found of large B cell lymphoma despite thorough sampling. Instead, there was a dense and permeative infiltrate of $CD3^+$ $CD8^+$ cytotoxic small T lymphocytes spanning the whole thickness of the gastric wall. *In situ* reverse transcription polymerase chain reaction for T cell receptor β-chain family did not detect a monoclonal T cell population. It was postulated that the cytotoxic T cells may represent an active host-immune response against the large B cell lymphoma that resulted in a complete regression. On questioning, the patient reported that he had taken mega doses of Lingzhi, which might have triggered the successful immune reaction.

Ganopoly has demonstrated immunomodulating and tumor inhibitory effects in *in vitro* and mouse models (Gao et al. 2002). A clinical trial was conducted to evaluate the efficacy and safety of ganopoly in patients with advanced cancer. One hundred and forty-three patients with advanced, previously treated cancer were enrolled. Eligibility criteria included confirmation of diagnosis, objectively measurable disease, Eastern Cooperative Oncology Group performance status of 0–2, life expectancy of 12 weeks or greater, no recent or concomitant anticancer therapy, and informed consent. Patients underwent evaluation of the extent of disease, QoL, hematologic, biochemical, and selected immune function studies at baseline and after 6 and 12 weeks of ganopoly therapy. Standard criteria were used to evaluate adverse events and response. Ganopoly was given orally at 1,800 mg three times daily. Of the 100 fully assessable patients, 46 patients (32.2%) had progressive disease (PD) before or at the 6-week evaluation point (range, 5 days to 6 weeks). Sixteen patients (11.2%) developed PD between 6 and 12 weeks of therapy. No objective (partial or complete) responses were observed, but 38 of 143 patients (26.6%) had stable disease (SD) for 12 weeks or more (range, 12–50 weeks). There was no significant change in the FACT-G scores in 85 assessable patients. However, palliative effects on cancer-related symptoms, such as sweating and insomnia, were observed in many patients. In the group of patients with SD, FACT-G scores improved in 23 patients, were unchanged in 5 patients, and declined in 1 patient. No significant changes of the selected immune function parameters were observed in 75 assessable patients. However, in the group of 32 patients with SD for 12 weeks or more, Ganopoly significantly increased lymphocyte mitogenic reactivity to concanavalin A and phyto-hemagglutinin by $28 \pm 7.3\%$ ($p < 0.05$) and significantly enhanced NK cell activity by $25 \pm 5.9\%$ ($p < 0.05$). The results indicate that ganopoly may have an adjunct role in the treatment of patients with advanced cancer, although objective responses were not observed in this study.

15.3.8 Yunzhi

Yunzhi (*Coriolus versicolor* mushroom, Fig. 15.2) has been shown recently the most promising source for cancer prevention and therapy, probably due to its activity in regulating the immune system. Several botanicals were tested for their

immune enhancing activity using a subcutaneous immunization model of cell surface carbohydrate expression in cancer cells (Ragupathi et al. 2008). The *Coriolus versicolor* raw water extract (especially purified polysaccharide-K, PSK, from it) was found to display consistent and significant immune enhancement activity superior to all other compounds tested. It was also reported that the *Coriolus versicolor* has shown anticancer activity with positive results in the treatment of *in vitro* and *in vivo* experimental models (Jiménez-Medina et al. 2008). The immunomodulatory capacity is the most important and widely reported property of PSK, although other mechanisms have been reported including working as antioxidant; as inhibitor of metalloproteinases and other enzymes involved in tumor extracellular matrix (Jiménez-Medina et al. 2008). Several randomized clinical trials have demonstrated that PSK has great potential in adjuvant cancer therapy, with positive results in the adjuvant treatment of gastric, esophageal, colorectal, breast and lung cancers (Sakamoto et al. 2006; Ueda et al. 2006). Sakamoto et al. reported double blind trials on 1,094 patients with colorectal cancer, using PSK from *Coriolus versicolor*. Although traditional medicine offers little help for colon cancer patients, PSK showed a remarkable enhancement of the patient's white blood cells, even in advanced colon cancer cases. The results of this study suggest that adjuvant immunochemotherapy with PSK can improve both survival and disease-free survival of patients with curatively resected colorectal cancer. A randomized, double-blind, placebo-controlled, crossover study with 100 healthy volunteers demonstrated that regular consumption of capsules containing Yunzhi (50 mg/kg) and Danshen (20 mg/kg) could be beneficial for immunological functions by potential enhancement of cell-mediated immunity without any adverse effects (Wong et al. 2004). In another study using the same combination, Yunzhi and Danshen were shown to be beneficial for promoting immunological function in post-treatment of breast cancer patients (Wong et al. 2005).

15.3.9 Xianggu

The shiitake mushroom (*Lentinus edodes*) has been cultivated as medicinal foods in Asian countries for over 6,000 years. It is called Xianggu or Xiang xun (Fig. 15.2) in Chinese. It shows a wide spectrum of health benefits, used medicinally for diseases involving depressed immune function (including AIDS), cancer, environmental allergies, fungal infection, frequent flu and colds, bronchial inflammation, heart disease, hyperlipidemia (including high blood cholesterol), hypertension, infectious disease, diabetes, hepatitis and regulating urinary inconsistencies (Bisen et al. 2010).

Lentinus edodes has been reported to have cancer-preventing properties (Fang et al. 2006). A number of β-glucans, for example pleuran from *Lentinus edodes*, have shown marked anticarcinogenic activity (Rop et al. 2009). A polysaccharide in *Lentinus edodes* called lentinan (1,3-β-D-glucan) boosts the immune system, helping to fight the flu and other viruses (Kaneko and Chihara 1992). Lentinan has anticancer effects that suppress colon cancer cells and inhibit the proliferation of leukemia cells (McCormack et al. 2010). Lentinan also promotes the development of reticular cells, which are immune system cells ingesting bacteria as well as cancerous cells, and

T lymphocytes (Ogawa et al. 1994; Yoshino et al. 2000). Xianggu also contains a potent antioxidant, L-ergothioneine, which may help protect normal cells against free radicals induced cell damage (Deiana et al. 2004). However, the components of *Lentinus edodes* were found to be ineffective against prostate cancer in a clinical trial (deVere White et al. 2002). Thus, treatment with these mushrooms or its extracts should not substitute for appropriate medical care for cancer, at least before substantial evidence for its standardization in preparation and efficacy has been demonstrated.

15.4 TIM as Cancer Chemopreventive Agents

15.4.1 Triphala

Triphala (Fig. 15.3) is the most commonly used Indian Ayurvedic herbal formulation, consisting of equal parts of three medicinal dried plant fruits *Emblica officinalis*, *Terminalia belerica*, and *Terminalia chebula*. It is an important medicine of the "Rasayana" group of Ayurveda and is believed to promote immunity, health and longevity. Rich in antioxidants, Triphala plays an essential role in the treatment of a

Fig. 15.3 Representative cancer chemopreventive herbs from traditional Indian medicine

wide variety of conditions such inflammation, anemia, constipation, asthma, jaundice, chronic ulcers and AIDS (Jagetia et al. 2002). Gallic acid and ascorbic acid (Table 15.2) are found to be the major ingredients of Triphala (Singh et al. 2008). There is a growing body of evidence in literature of Triphala being effective in the chemoprevention of a variety of cancers.

One of the first reports on cancer chemopreventive potential of Triphala showed that when included in the diet, it significantly reduced the benzo[*a*]pyrene-induced forestomach papillomagenesis in mice (Deep et al. 2005). In short and long term treatment with Triphala, tumor incidences decreased significantly when administered as the triple combination in comparison to the individual components of the medication. Triphala also significantly increased the antioxidant status of animals which might have contributed to the chemoprevention. It was inferred that the concomitant use of multiple agents seemed to have a high degree of chemoprevention potential.

The cytotoxic effects of Triphala were also investigated on two human breast cancer cell lines differing in their p53 status (Sandhya and Mishra 2006). *In vitro* studies showed that MCF-7 breast cancer cells with wild type p53 was more sensitive to Triphala than T-47 D, which is p53 negative. Triphala was also found to induce dose and time dependent increase in intracellular ROS in both cell lines. Inhibition of anti-proliferative ability of Triphala by antioxidants suggests a role for Triphala-induced ROS in the induction of apoptosis. It was concluded that p53 status of cancer cells formed an important factor in predicting the response of cancer cells to pro-oxidant drugs.

The acetone extract of Triphala showed a significant cytotoxic effect on Shionogi 115 and MCF-7 and PC-3 and DU-145 prostate cancer cells (Kaur et al. 2005). The suppression of the growth of cancer cells was determined to be due to gallic acid, a major polyphenol in Triphala.

Recently, the effect of Triphala against pancreatic cancer cells was demonstrated in a study wherein the molecular mechanism of Triphala against human pancreatic cancer in the cellular and *in vivo* models was elucidated (Shi et al. 2008). Exposure of Capan-2 cells to the aqueous extract of Triphala for 24 h resulted in the significant decrease in the survival of cells in a dose-dependent manner with an IC_{50} of 50 μg/ml. Similarly, Triphala induced apoptosis in another pancreatic cancer cell line BxPC-3 by activating ERK. Triphala was administered orally to nude mice implanted with Capan-2 xenograft. Reduced tumor-growth in Triphala fed mice was due to increased apoptosis in tumor cells, which was associated with increased activation of p53 and ERK. The preclinical studies demonstrated that Triphala was effective in inhibiting the growth of human pancreatic cancer cells in both cellular and *in vivo* models.

15.4.2 Turmeric

Turmeric (Fig. 15.3), also called Indian saffron, is the root powder of *Curcuma longa,* and has long been used in TIM as a treatment for inflammatory and other conditions. The same herb is listed in TCM as Jiang hua. Three curcuminoids, i.e.

curcumin (diferuloylmethane; the primary constituent responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin (Table 15.2) are the main constituents of Turmeric, along with volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins (Jurenka 2009). Curcumin is insoluble in water and ether but is soluble in oil, ethanol, dimethylsulfoxide and other organic solvents. In recent years, curcumin has been the focus of investigation as a therapeutic agent in a variety of disorders such as inflammatory bowel disease, pancreatitis, as well as certain types of cancers. Starting from cell culture studies, curcumin research has evolved into more and more clinical studies to gain a deeper understanding of the therapeutic potential of this naturally occurring product.

Curcumin inhibits cancer development and progression, targeting multiple steps in the pathway to malignancy. It has activity as both a blocking agent, inhibiting the initiation step of cancer by preventing carcinogen activation, and as a suppressing agent, inhibiting malignant cell proliferation during promotion and progression of carcinogenesis. Curcumin is thought to suppress NF-κB activation and pro-inflammatory gene expression by blocking phosphorylation of inhibitory factor IκB. Suppression of NF-κB activation subsequently down-regulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis (Jobin et al. 1999). In an animal model of inflammation, curcumin also inhibited arachidonic acid metabolism and inflammation in mouse skin epidermis *via* down-regulation of the COX and lipoxygenase pathways (Huang et al. 1991).

Although more clinical outcomes are expected in the near future regarding the effectiveness of curcumin against cancer, current data on clinical trials published in peer-reviewed literature utilizing curcumin for chemoprevention or for cancer therapy are somewhat limited (Jurenka 2009). A Phase I clinical trial investigated the use of curcumin as a chemopreventive agent in 25 patients with various types of high-risk or premalignant lesions. After an initial dose of 500 mg curcumin daily, the dose was increased to as much as 8 g daily for 3 months. Histological improvement of lesions was seen in one of two patients with recently resected bladder cancer, two of seven patients with oral leukoplakia, one of six patients with intestinal metaplasia of the stomach, one of four patients with carcinoma *in situ* and two of six patients with Bowen's disease. Histological improvement of precancerous lesions was observed in one of four patients with cervical intraepithelial neoplasm (decreased hyperkeratosis and parakeratosis), one of six patients with intestinal metaplasia of the stomach (fewer goblet cells), one of two patients with recently resected bladder cancer (decreased dysplasia and inflammation), two of seven patients with oral leukoplakia, and two of six patients with Bowen's disease (Cheng et al. 2001). In conclusion, this study demonstrated that curcumin is not toxic to humans up to 8 g/day when taken by mouth for 3 months. These results also suggested a biological effect of curcumin in the chemoprevention of cancer.

Additional studies on colorectal cancers have also been conducted; Sharma et al. (Sharma et al. 2001, 2004) conducted two separate clinical trials exploring curcumin's effect on malignancies and tumor marker levels. In one trial (Sharma et al. 2004), 15 patients with advanced colorectal cancer were given a low-dose (440–2,200 mg daily) Turmeric extract (equivalent to 36–180 mg curcumin) for up to

4 months. The activity of GST and levels of a DNA adduct (M1G) formed by malondialdehyde, a product of lipid peroxidation and prostaglandin biosynthesis, were measured in patients' blood cells. Oral curcuma extract was well tolerated and dose-limiting toxicity was not observed. Neither curcumin nor its metabolites were detected in blood or urine, but curcumin was recovered from feces. Ingestion of 440 mg of Turmeric extract for 29 days was accompanied by a 59% decrease in lymphocytic GST activity. At higher dose levels, this effect was not observed. Leukocytic MlG levels were constant within each patient and unaffected by treatment. Radiologically, stable disease was demonstrated in five patients for 2–4 months of treatment. The results suggested that: (a) Turmeric extract can be administered safely to patients at doses of up to 2.2 g daily, equivalent to 180 mg of curcumin; (b) Curcumin has low oral bioavailability in humans and may undergo intestinal metabolism; and (c) Larger clinical trials of curcuma extract are merited.

In another clinical trial (Sharma et al. 2001), researchers used a higher potency curcuminoid preparation, each capsule containing 450 mg curcumin, 40 mg demethoxycurcumin, and 10 mg bisdemethoxy-curcumin. Fifteen patients with advanced colorectal cancer were given curcuminoid doses of 450–3,600 mg daily for up to 4 months. Blood and imaging tests were performed at baseline and various points throughout the trial. In six patients, given at the 3,600 mg dose, mean PGE2 levels measured after 29 days of treatment decreased by 46% compared to baseline. PGE2 is an end product of COX-mediated oxidation that has been shown to stimulate growth of human colorectal cancer cells. In addition, two patients (one taking 900 mg, the other taking 1,800 mg) demonstrated stable disease as determined *via* CT scan or MRI after 2 months.

Another clinical trial investigated curcumin's effects in patients with colorectal cancer at doses of 450, 1,800, or 3,600 mg daily for 7 days (Garcea et al. 2005). The aim of this study was to determine if these doses resulted in pharmacologically active levels of curcumin in colorectal tissue or had any effect on tissue levels of the oxidative DNA adduct M1G, a mutagenic byproduct of lipid peroxidation, or COX-2 markers of DNA damage and inflammation. The highest dose (3,600 mg) resulted in a significant decrease in M1G from 4.8 ± 2.9 to 2.0 ± 1.8 per 107 nucleotides. In another clinical trial, curcumin stabilized disease progression in patients with advanced pancreatic cancer (Dhillon et al. 2008). Twenty-one patients received 8 g curcumin daily until disease progression. Serum cytokine levels as well as NF-κB and COX-2 levels in peripheral blood mononuclear cells were monitored. One patient achieved disease stabilization for 18 months. Interestingly, a second patient experienced significant increases in serum cytokine levels (4- to 35-fold) accompanied by a brief, but marked tumor regression (73%). Down-regulation of NF-κB and COX-2 were also observed.

Lal et al. (1999) administered curcumin orally to patients suffering from chronic anterior uveitis (CAU) at a dose of 375 mg three times a day for 12 weeks. They were divided into two groups: one group of 18 patients received curcumin alone, whereas the other group of 14 patients, in addition received anti-tubercular treatment. The patients in both the groups started improving after 2 weeks of treatment. All the patients who received curcumin alone improved, whereas the group receiving anti-tubercular therapy along with curcumin had a response rate of 86%. Follow-up of

all the patients for the next 3 years indicated a recurrence rate of 55% in the first group and of 36% in the second group. The efficacy of curcumin and recurrences following treatment were comparable to corticosteroid therapy, which is presently the only available standard treatment for this disease.

Curcumin has also been used for the treatment of patients suffering from idiopathic inflammatory orbital pseudo-tumors (Lal et al. 2000). Curcumin was administered orally at a dose of 375 mg/3 times/day orally for a period of 6–22 months in eight patients. They were followed-up for a period of 2 years at 3-month intervals. Five patients completed the study, of which four recovered completely and one experienced some persistent limitation of movement but the swelling regressed completely. No side effect was noted in any patient and there was no recurrence. The study suggests that curcumin could be used as a safe and effective drug in the treatment of idiopathic inflammatory orbital pseudo-tumors.

Currently there are several ongoing clinical trials investigating the benefits of curcumin as a therapy for various cancers (Jurenka 2009; Hatcher et al. 2010). Table 15.3 lists ongoing clinical trials investigating the anticancer potential of curcumin. Based on these studies, a better understanding of curcumin's efficacy for chemoprevention and treatment of active cancer is expected.

15.4.3 Neem

The Neem tree or margosa has the botanical name *Azadirachta indica* which literally means "the free tree of India". A sample of its leaf powder is shown in Fig. 15.3. Numerous active compounds have been isolated from Neem (Subapriya and Nagini 2005). Some of the most studied include gedunin, sodium nimbinate, salannin, nimbin, ninbidiol, quercetin, nimbidin, and azadirachtin (Table 15.3). Analysis also reveals the presence of carotenoids, nutritive compounds being hailed for their ability to ward off many types of cancer. Neem contains multiple active compounds that work simultaneously *via* different mechanisms. One of these documented mechanisms is apoptosis. Neem has also been shown to produce substantially higher levels of antioxidants, including the carcinogen-detoxifying GSH. Recently, Neem has shown impressive efficacy against a wide variety of human cancer cell lines, and animal models for human cancers that include colon, stomach, Ehrlich's carcinoma, lung, liver, skin, oral, prostate, and breast cancers (Vinothini et al. 2009).

In addition to studies showing that pretreatment with Neem is highly protective against cancer in animals and demonstrating the efficacy of Neem as a stand-alone treatment, recent reports suggest that Neem pretreatment also enhances the activity while reducing the side effects of some conventional cancer treatments. Much research obviously remains to be done before Neem can be recommended for human use, but the consistently spectacular results from these *in vitro* and preclinical studies have already inspired tremendous enthusiasm and hope.

Vinothini et al. evaluated the chemopreventive potential of the ethyl acetate fraction and methanol fraction of Neem leaf on 7,12-dimethylbenz(*a*)anthracene

Table 15.3 Clinical trials on curcumin being conducted around the world

Clinical trial identifier	Condition	Site	Intervention	Trial phase	Completion date
NCT00365209	Colon cancer prevention	Chao Family Comprehensive Cancer Center	Curcumin	Phase 2	Unknown
NCT00118989	Colon cancer prevention	University of Pennsylvania	Curcuminoid complex, 4 g daily	Phase 2	June 2009
NCT00641147	Familial adenomatous polyposis	Johns Hopkins University	Curcumin, 700 mg twice daily	Phase 2	March 2013
NCT00745134	Rectal cancer	MD Anderson Cancer Center	Curcumin, 4 g daily, Capecitabine	Phase 2	July 2010
NCT00486460	Pancreatic cancer	Tel-Aviv Sourasky Medical Center	Gemcitabine, curcumin, celebrex	Phase 3	Unknown
NCT00094445	Pancreatic cancer	MD Anderson Cancer Center	Curcumin, 8 g daily	Phase 2	December 2009
NCT00113841	Multiple myelomas	MD Anderson Cancer Center	Curcumin + Bioperine, 2 g twice daily	Pilot Study	December 2008
NCT00689195	Osteosarcoma	Tata Memorial Hospital, Mumbai, India	Curcumin and Ashwagandha	Phase 1 and 2	May 2012
NCT00475683	Oral mucositis-children on chemotherapy	Hadassah Memorial Hospital, India	Curcumin liquid extract, 5 ml in 50 ml water, mouthwash, three times daily	Phase 3	December 2009
NCT00176618	Colon cancer	University of Medicine and Dentistry, NJ	Curcumin	–	Completed
NCT00927485	Intestinal cancer	University of Puerto Rico	Curcumin	–	Ongoing
NCT00745134	Rectal cancer	MD Anderson Cancer Center	Curcumin	Phase 2	Ongoing
NCT00027495	Colorectal cancer	University of Michigan, NCI	Curcumin	Phase 1	Completed
NCT00192842	Pancreatic cancer	Rambam Medical Center, Haifa, Israel	Curcumin with gemcitabine	Phase 2	Ongoing

(DMBA)-induced rat mammary carcinogenesis (Vinothini et al. 2009). Administration of both the ethyl acetate fraction and methanol fraction at 10 mg/kg effectively suppressed tumor incidence. Chemoprevention by Neem leaf fractions was associated with modulation of hormone and receptor status, xenobiotic-metabolizing enzymes, and lipid and protein oxidation, with up-regulation of antioxidants, inhibition of oxidative DNA damage, protein modification, and cell proliferation, and induction of apoptosis. The ethyl acetate fraction was more effective than the methanol fraction in modulating multiple molecular targets.

Sarkar et al. studied the involvement of NO release in CEAM phi NLGP (carcinoembryonic antigen pulsed macrophages with Neem leaf glycoprotein) and its relationship with vaccine induced type 1 immune response (Sarkar et al. 2009). Obtained results clearly demonstrated the interdependence of two antitumor immune functions, namely, NO production and generation of type 1 immune response. Understanding of the mechanism of this NO related immune modulation would have great impact in proposing CEAM phi NLGP vaccine in clinic for the treatment of CEA^+ tumors.

A study was designed to evaluate the chemopreventive potential of the neem limonoids, azadirachtin, and nimbolide based on *in vitro* antioxidant assays and *in vivo* inhibitory effects on DMBA-induced hamster buccal pouch carcinogenesis (Priyadarsini et al. 2009). Both azadirachtin and nimbolide exhibited concentration-dependent anti-radical scavenging activity and reductive potential in the order: nimbolide > azadirachtin > ascorbate. Administration of both azadirachtin and nimbolide inhibited the development of DMBA-induced buccal pouch carcinomas by influencing multiple mechanisms including prevention of procarcinogen activation and oxidative DNA damage, up-regulation of antioxidant and carcinogen detoxification enzymes and inhibition of tumor invasion and angiogenesis. On a comparative basis, nimbolide was found to be a more potent antioxidant and chemopreventive agent and offers promise as a candidate agent in multi-targeted prevention and treatment of cancer. In another report, the cytotoxic effects of nimbolide, was studied on human choriocarcinoma (BeWo) cells (Harish Kumar et al. 2009). Treatment with nimbolide resulted in dose and time dependent inhibition of growth of BeWo cells with IC_{50} values of 2.01 and 1.19 mM for 7 and 24 h incubations respectively, accompanied by down-regulation of proliferating cell nuclear antigen. The results of the study suggested that nimbolide has potential in cancer prevention and therapy based on its anti-proliferative and apoptosis-inducing effects. Roy et al. (2007) reported that nimbolide was found to have anti-proliferative activity against several cancer cell lines. Treatment of cells with 0.5–5.0 μM concentrations of nimbolide resulted in moderate to very strong growth inhibition in U937, HL-60, THP1, and B16 cell lines. Quantification of the expression of phosphatidylserine in the outer cell membrane showed that doses of nimbolide higher than 0.4 μM exerted remarkable lethality, with over 60% of cells exhibiting apoptotic features after exposure to 1.2 μM nimbolide. The anti-proliferative effect of nimbolide and its apoptosis inducing property raise hope for its use in anticancer therapy by enhancing the effectiveness of cell cycle disruption.

A Neem leaf preparation was investigated for its role in the induction of tumor cell apoptosis to elucidate the mechanism of Neem leaf preparation-mediated

immunoprophylaxis in tumor growth restriction (Bose et al. 2007). An enzyme linked immunosorbant assay revealed the presence of cytotoxic cytokines, IFN-gamma and TNF-alpha, in the Neem leaf preparation culture supernatant. The inhibition of secretion of IFN-gamma and TNF-alpha in the Neem leaf preparation culture supernatant caused a significant decrease in tumor cell apoptosis. Furthermore, stimulation of these tumor cells with Neem leaf preparation culture supernatant resulted in up-regulation of the caspase-3 and down-regulation of the Bcl-2 and cyclin D1. These observations suggested that Neem leaf preparation could induce tumor cellular apoptosis by releasing cytotoxic cytokines from human PBMC.

15.4.4 Guggulu

Guggulu (Fig. 15.3), the gum resin from the tree *Commiphora mukul*, has been used in TIM for centuries to treat ailments such as obesity, bone fractures, arthritis, inflammation and cardiovascular disorders. The active substances in Guggulu are the pregnane plant sterols E- and Z-guggulsterone (Table 15.2), which have been shown to lower cholesterol and triglycerides. However, they have also been shown to have potent anti-inflammatory effects (Kaul and Kapoor 1989). Guggulsterone blocks NF-κB signaling pathway by targeting the IκB kinase complex and suppresses the activation of constitutive and inducible NF-κB, tumor promoters (phorbol myristate acetate and okadaic acid), hydrogen peroxide and cytokines (interleukin 1B and tumor necrosis factor) (Shishodia and Aggarwal 2004; Xiao and Singh 2008). Previous studies have shown that E-guggulsterone inhibits the growth of PC-3, DU145, and LNCaP human prostate cancer cells by causing apoptosis initiated by ROS-mediated activation of c-Jun NH_2-terminal kinase (Singh et al. 2005, 2007). Anti-proliferative and/or apoptosis-inducing effects of guggulsterone have also been documented in lung, acute myeloid leukemia and breast cancer cells (Samudio et al. 2005).

Guggulsterone has also demonstrated, in recent studies, the inhibition of angiogenesis *in vitro* and *in vivo* which has been implicated in the pathogenesis of many diseases, including cancer. *In vivo* studies conducted on male nude mice inhibited angiogenesis in DU145-Matrigel plug assay as evidenced by a decrease in tumor burden, microvessel area and VEGF-R2 expression. Hence, the authors postulated that guggulsterone inhibited angiogenesis by suppressing the VEGF-VEGF-R2-Akt signaling axis and hence was effective against prostate cancer (Samudio et al. 2005).

Similarly, studies showing the treatment of head and neck squamous cell carcinoma (HNSCC) cells with guggulsterone induced apoptosis and cell cycle arrest and enhanced the efficacy of frontline treatment regimens using erlotinib, cetuximab and cisplatin. *In vivo* treatment with guggulu resulted in decreased rates of tumor growth and enhancement of cetuximab's activity (Leeman-Neill et al. 2009). Recently, guggulsterone demonstrated the induction of apoptosis in HT-29 colon

cancer cell lines by activating caspase-3 and -8, and inhibited tumor growth in murine colorectal cancer xenografts in mice (An et al. 2009).

The effects of guggulsterone on colon cancer cells and the underlying molecular mechanisms related to angiogenesis were investigated (Kim et al. 2008). Guggulsterone significantly reduced cell viability in colon cancer cells in a dose dependent manner and blocked VEGF, ARNT, and STAT3 expression prominently in hypoxic conditions. The recruitment of STAT3 and ARNT, but not HIF-1α, to the VEGF promoter was inhibited by guggulsterone treatment. The results of this study suggest that guggulsterone not only induces apoptosis, but also inhibits angiogenesis and metastasis in colon cancer cells by blocking STAT3 and VEGF expression, suggesting its therapeutic potential in the treatment of colorectal cancer.

A report on the anticancer effect and mechanism of Guggulu against human prostate cancer cells was reported (Xiao et al. 2011). Treatment with Guggulu significantly inhibited viability of human prostate cancer cell line LNCaP (androgen-dependent) and its androgen-independent variant (C81) with an IC_{50} of 1 μM (24 h treatment) at pharmacologically relevant concentrations standardized to its major active constituent Z-guggulsterone. The Guggulu induced growth inhibition correlated with apoptosis induction as evidenced by an increase in cytoplasmic histone-associated DNA fragmentation and sub-G0/G1 DNA fraction, and cleavage of poly(ADP-ribose) polymerase.

15.4.5 Sapthaparna

Sapthaparna, an herbal preparation of *Alstonia scholaris*, has been used for generations in India for the treatment of diseases such as syphilis-related insanity, epilepsy, and ulcers. The bark is the most extensively used part of the tree and is used in many compound herbal formulations (Keawpradub et al. 1997). Sapthaparna contains several alkaloids, including echitamine (Table 15.3). In recent times, the anticancer effects of Sapthaparna were investigated whereby the chemopreventive effect of various doses of a hydro-alcoholic extract of Sapthaparna was studied on the benzo(*a*)pyrene (BaP)-induced stomach carcinoma in female mice (Jagetia et al. 2003). The tumor incidence was reduced by 6.7%. Similarly, the tumor multiplicity reduced significantly. Sapthaparna treatment not only reduced the frequency of micronuclei in the splenocytes bearing one micronuclei but also cells bearing multiple micronuclei indicating the efficacy of Sapthaparna in inhibiting mutagenic changes induced by BaP.

In another study, the anticancer effect of various doses of an alkaloid fraction of Sapthaparna, was studied *in vitro* in cultured human neoplastic cell lines (HeLa, HepG2, HL-60, KB, and MCF-7) and in Ehrlich ascites carcinoma bearing mice (Jagetia and Baliga 2006). Exposure of cells to Sapthaparna for 4 h resulted in only 25% viability of cells. *In vivo* studies with tumor bearing mice administered Sapthaparna extract daily for 9 consecutive days caused a dose dependent remission of the tumor up to 240 mg/kg. 20% of the animals survived up to 120 days post tumor cell inoculation as against no survivors in the saline treated control group.

Cancer occurs in 2–10 pregnancies out of 1,000, and if chemotherapeutic agents cross the placental barrier, the fetus can be exposed adversely. Thus, the teratogenic effect of a hydroalcoholic extract of Sapthaparna was studied in pregnant Swiss albino mice administered with increasing doses ranging from 0 to 480 mg/kg Sapthaparna extract (Jagetia and Baliga 2003). The administration of 60, 120, 180, and 240 mg/kg Sapthaparna extract to the pregnant mice on day 11 did not induce mortality, congenital malformations, or alter the normal growth patterns. A further increase in Sapthaparna extract dose up to 360 or 480 mg/kg resulted in a dose dependent increase in the mortality, growth retardation, and congenital malformations, characterized mainly by bent tails and syndactyly. This study indicated that Sapthaparna extract treatment caused teratogenic effect only at doses above 240 mg/kg (420% of LD_{50}). Lower doses had no developmental toxicity hence can be investigated as alternative to potent, teratogenic drugs.

The chemomodulatory activity of Sapthaparna extract was studied in combination with berberine, a topoisomerase inhibitor, in Ehrlich ascites carcinoma-bearing mice (Jagetia and Baliga 2004). The combination of 180 mg/kg of Sapthaparna extract with 8 mg/kg of berberine showed the greatest antitumor effect; the number of tumor-free survivors was greater, and the median survival time and the average survival time increased up to 47 and 40.5 days, respectively, when compared with either treatment alone.

The chemopreventive and anti-oxidative properties of Sapthaparna have also been tested skin carcinogenesis. One such study (Jahan et al. 2009) on skin carcinogenesis was conducted using a single application of DMBA, and 2 weeks later, promoted by repeated application of croton oil (1% in acetone/three times a week) till the end of the experiment (16 weeks) in Swiss albino mice. The tumor incidence, tumor yield, tumor burden and cumulative number of papillomas were found to be higher in the carcinogen treated control as compared to Sapthaparna-co-treated animals. This study demonstrated the chemopreventive potential of Sapthaparna extract in DMBA-induced skin tumorigenesis in Swiss albino mice.

15.5 Challenges and Strategy for the Development of Cancer Chemopreventive Agents from TCM and TIM

Many herbs from TCM and TIM or other traditional medicines have been recorded for thousands of years for their energizing and healing properties in humans. However, translating traditional medicines into acceptable evidence-based Western therapies is still difficult. The inconsistency in manufacturing standards, criteria of purity, and lack of well-designed clinical trials make evaluation of clinical efficacy and toxicity by the Western standards difficult. Nevertheless, progress is being made and it is foreseeable that one day standardized medical products developed from traditional medicines will enter the main stream Western health care.

As we can conclude from this survey of literature, there are two general approaches to study the cancer chemopreventive effect of TCM and TIM: the

mixture approach and the single compound approach. Both have advantages and disadvantages. The mixture approach is more "holistic", a natural trait of the traditional medicine. However, quality control and reproducibility are serious issues. The single compound approach is usually recognized as a reductionist Western approach. Although it's more "scientific", it loses the synergism from the intricacy interactions among the various components with many biological pathways. To solve this dilemma, we propose here a three-step integrated strategy to facilitate the discovery and development of cancer chemopreventive agents from TCM and TIM:

Step (1) Identify major TCM and TIM which show significant cancer chemopreventive effects as mixtures;

Step (2) Clarify the specific chemopreventive mechanisms by using 2–3 major isolated single components;

Step (3) Recombine these single components to obtain a cocktail product which is more efficacious than individual component while with less side effects due to reduced doses for each individual component.

15.6 Conclusions

TCM and TIM have been used to prevent and treat human diseases for thousands of years. Due to availability of a vast database of information collected over this long period of time, it is possible to identify remedies with low side effects, thus making them extremely suitable for long term use as oral or topical chemopreventive agents. The availability of thousands of single entities as well as combination formulas in TCM and TIM and in particular those with known anti-inflammatory properties provide a rich source for identifying effective chemopreventive agents. Even though cancer prevention using TCM and TIM is still in its infancy, results from Danshen, Huang Jiang, Triphala, and particularly Turmeric are very promising. It is foreseeable that in the years to come, with improved investigative strategies, more and more herbal medicine will be screened for cancer chemoprevention and several non- or low-toxic TCM and TIM preparations and their recombined active components will be identified and clinically used as effective chemopreventive agents for various types of cancer in humans, especially in high risk populations.

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