Chapter 9
Modulation of Proteasome Pathways by Nutraceuticals

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Abstract The proteasome is a multicatalytic proteinase complex, the inhibition of which has been associated with induction of apoptosis, anti-tumorigenesis, and chemosensitization of tumor cells to the conventional chemotherapeutics agents and radiation. Therefore, inhibition of the proteasome pathway could be a novel approach for the prevention and treatment of cancer. Proteasome inhibitors mediate the antitumor effect through modulation of transcription factors, cell cycle regulatory proteins, and pro- and anti-apoptotic proteins. Although numerous proteasome inhibitors have been rationally designed, most of them not only are enormously expensive but also produce serious side effects. Currently, numerous nutraceuticals such as curcumin, sesamin, quercetin, silybinin, sulforaphane, resveratrol, tubocapsenolide A, CDDO-Me, γ-tocotrienol, apigenin, ferulic acid, betulinic acid, anacardic acid, genistein, withaferin A, emodin, withanolide, and gambogic acid derived from fruits, vegetables, spices, nuts, and legumes have shown promise as proteasome inhibitors, which may contribute to their anticancer activities. Although the mechanism of proteasome inhibition by nutraceuticals is different, it plays a crucial role against cancer. In this chapter, we discuss the targets of these nutraceuticals in the proteasome pathway. How inhibition of the proteasome pathway by these natural agents contributes to their anticancer activities is also discussed.

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W.C.S. Cho (ed.), *Cancer Chemoprevention and Treatment by Diet Therapy*, Evidence-based Anticancer Complementary and Alternative Medicine 5,
DOI 10.1007/978-94-007-6443-9_9,

9.1 Introduction

Protein metabolism involves both synthesis and degradation of proteins (Goldberg and Dice 1974). Synthesis of proteins occurs through central dogma, which include transcription (making of an RNA molecule off of a DNA template) and translation (construction of polypeptide from an RNA molecule). Degradation or elimination of proteins is mediated by two major intracellular devices, lysosomes and proteasomes. Lysosomes deal primarily with extracellular proteins, whereas proteasomes deal with endogenous proteins. The proteasome degradation pathway is essential for many cellular processes, including cellular differentiation (in which transcription factors and metabolic enzymes are degraded), cell cycling (in which cyclins are degraded to prepare for the next step in the cell cycle), regulation of gene expression, responses to oxidative stress, antigen processing for appropriate immune responses, inflammatory responses, and apoptosis (Mitch and Goldberg 1996; Cuervo and Dice 1998; Hershko and Ciechanover 1998; Ciechanover 2005). It also degrades proteins encoded by viruses and other intracellular pathogens and proteins that are folded incorrectly because of translation errors or encoded by faulty genes (Homma et al. 1994). Proteasomes play an important role in the immune system by generating antigenic peptides that are presented by the major histocompatibility complex (MHC) class I molecules (Groettrup et al. 2010).

9.2 Proteasomes

Proteasomes are subcellular organelles found throughout the cytosol, nucleus, endoplasmic reticulum (ER), and lysosomes of eukaryotic cells (Adams 2002). Structurally, proteasomes are cylindrical and composed of four rings stacked on top of each other. Each ring is composed of seven subunits. The two outer rings contain α subunits and do not have enzymatic activity, while the two inner rings comprising β subunits have the proteolytic activities. There are three major proteolytic activities in the β subunits: a chymotrypsin-like (CTL), a trypsin-like (TL) and a caspase-like activity. The most common form of the proteasome, 26S proteasome, contains one 20S core particle structure and two 19S regulatory caps. The core is hollow and provides an enclosed cavity in which proteins are degraded. The 19S components regulate the entry of proteins into the 20S proteasome (Coux et al. 1996). Openings at the two ends of the core allow the target protein to enter. Each end of the core particle associates with a 19S regulatory subunit that contains multiple ATPase active sites and ubiquitin binding sites. This subunit recognizes polyubiquitinated proteins and transfers them to the catalytic core (Wang and Maldonado 2006).

More than 80 % of a cell's unassembled, damaged, or misfolded proteins are processed by proteasomes (Coux et al. 1996). A cascade of enzymes are involved in this process, including ubiquitin-activating E1 enzymes, ubiquitin-carrier protein

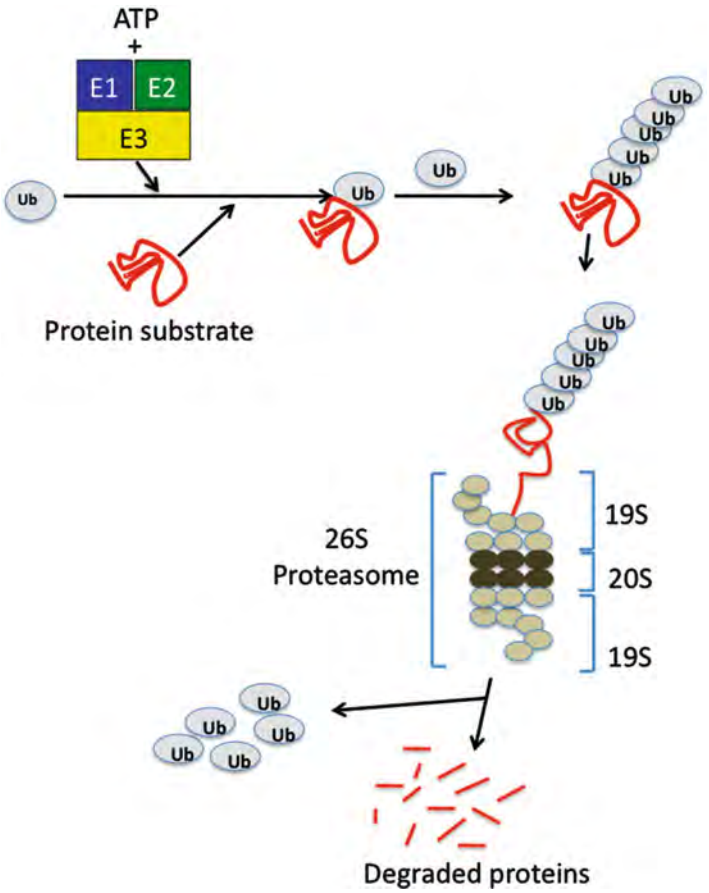

Fig. 9.1 The ubiquitin-proteasome pathway

E2 enzymes, and the ubiquitin-protein E3 ligases, which conjugate the ubiquitin residues to the target protein substrate for degradation. Proteasomes act on target proteins by attaching to another protein called ubiquitin. Degradation signals are generally hidden in a properly folded protein, but become accessible when the protein is misfolded or denatured. When these signals are exposed, enzymes add another small ubiquitin protein to the target called polyubiquitin-tagged proteins, which are then recognized by a receptor protein on the proteasome and the target protein is taken into the proteasome and digested by threonine proteases. The fragmented protein is then released from the proteasome (Rape and Jentsch 2002) (Fig. 9.1). These fragments are processed by intracellular peptidases to yield amino acids, which are then recycled into new proteins (Bochtler et al. 1999). Although the proteasome normally produces very short peptide fragments, in some cases these products are themselves biologically active and functional proteins, such as nuclear factor-κB (NF-κB) (Rape and Jentsch 2004).

9.3 Proteasome, Proteasome Inhibitors, and Cancer

Proteasomes control the half-life of several cell-signaling regulatory proteins. It is responsible for the degradation of all short-lived proteins and 70–90 % of all long-lived proteins, thereby regulating processes such as cell cycle progression and cell cycle arrest, transcription, DNA repair, angiogenesis, apoptosis, survival, growth and development, inflammation, and immunity. Since imbalances in proteasome-mediated protein degradation contribute to various human cancers, the proteasome might be a novel target for anticancer therapy (Pajonk and McBride 2001; Naujokat and Hoffmann 2002). However, inhibition of proteasome function leads to the accumulation of polyubiquitin-tagged proteins and the withdrawal of the cell from the cell cycle, followed by the induction of apoptosis in susceptible cells (Sterz et al. 2008; Driscoll and Dechowdhury 2010).

Several pharmacological inhibitors of the proteasome have been developed, including synthetic peptidyl aldehydes MG132, PSI, ALLN, ALLnV, ALLnM, CEP1612, and Z-LLF; bacterial compound lactacystin; dipeptidyl boronic acid PS-341 (also known as bortezomib); and several natural products (Lee and Goldberg 1998). Proteasome inhibitors have shown to induce apoptosis in some cells and seem to prevent it in others. In proliferating cells, proteasome inhibitors appear to induce apoptosis but they appear to protect quiescent or terminally differentiated cells from apoptosis (Drexler 1997). Lactacystin induced apoptosis of U937 human leukemia and Jurkat cells (Imajoh-Ohmi et al. 1995; Naujokat et al. 2003), MG132 showed cell death in MOLT-4 human leukemia (Shinohara et al. 1996), and ALLN induced apoptosis of human prostate carcinoma (Herrmann et al. 1998). Bortezomib has been shown to have anti-tumor activity in myeloma and lymphoma (Tobinai 2007). In addition, numerous other proteasome inhibitors act as anticancer agents.

How proteasome inhibitors induce apoptosis of cancer cells is not fully understood. Various reports have suggested that these inhibitors act through increasing p53 activity, fostering the accumulation of p27 and p21 molecules, enhancing pro-apoptotic proteins, activating stress-activated protein kinases (Meriin et al. 1998), inducing caspases (Almond et al. 2001), and decreasing NF-κB activity (Russo et al. 2001). In addition, proteasome inhibitors increase unfolded proteins, resulting in activation of ER stress-induced signaling pathways and induction of apoptosis (Bratton and Cohen 2001). Although proteasome inhibitors have been shown to induce apoptosis in cancer cells, only limited reports have suggested the selectivity of proteasome inhibitors to tumor cells. The susceptibility of tumor cells to proteasome inhibitors may be because of their high proliferation rate. Another report suggested that the tumor-specific killing by proteasome inhibitors might be due to the expression of oncogenes such as c-myc that deregulate cell proliferation and also induce apoptosis (Soengas et al. 1999). Alternatively, in some cancer cells, there may be either deficiencies in, or excessive proteasome degradation of, proteins that inhibit cell growth or induce apoptosis, such as p27KIP1, p53, and B-cell lymphoma-2 (Bcl-2)-associated X protein (Bax) (Lloyd et al. 1999; Li and Dou 2000).

Recently, natural compounds have been shown to act as proteasome inhibitors, which may lead to killing and increased sensitivity of cancer cells to conventional agents and thus inhibition of tumor growth. To date, over 60 natural products that inhibit the ubiquitin-proteasome pathway have been identified. Several of these natural products have been developed into anticancer drug candidates, and one proteasome inhibitor has already been approved for the treatment of multiple myeloma (Schneekloth and Crews 2011).

9.4 Natural Compounds as a Regulator of Proteasome Degradation Pathway

Numerous natural compounds derived from spices, fruits and vegetables, legumes, nuts, and microbial metabolites have been shown to be potent proteasome inhibitors (Fig. 9.2). These proteasome inhibitors either downregulate the expression of cell-proliferative, survival, invasion, metastatic and oncogenic proteins (Table 9.1) or upregulate apoptotic and tumor-suppressor proteins (Table 9.2). Thus, these natural proteasome inhibitors potentially can be used not only as chemopreventive and chemotherapeutic agents, but also as tumor sensitizers to conventional radiotherapy and chemotherapy. In this section, we summarize the proteasome inhibitory activity of several natural compounds and will discuss the potential use of these compounds for the prevention and treatment of human cancers.

9.4.1 Spices

In addition to spices' long history of uses as traditional medicine, experimental and clinical studies have proven their efficacy against several human diseases through modulating several cell signaling pathways, including inhibition of the ubiquitin proteasome pathway. Among spices, curcumin (an active component of turmeric) is one of the most often described and best-known natural proteasome inhibitors, with cell growth arrest and cell death inducing as observed in several tumor cell lines and animal models. It mediates degradation as well as restoration of several proteins in different *in vitro* and *in vivo* models (Table 9.1). A study using three breast cancer cell lines (MDA-MB-231, MDA-MB-436, and Hs578T) showed that curcumin mediates its cell cycle inhibitory activities by blocking the CTL activity of the proteasome *in vitro*. It is suggested that curcumin might mediate G1 arrest and possible cytostasis and apoptosis by blocking the proteasome activity and upregulating the p21 protein in breast cancer cells (Efuet and Keyomarsi 2006). Proteasome-mediated downregulation of cyclin E and upregulation of cyclin-dependent kinase (CDK) inhibitors may also contribute to the antiproliferative effects of curcumin by arresting the cells at G1 phase of cell cycle as observed in

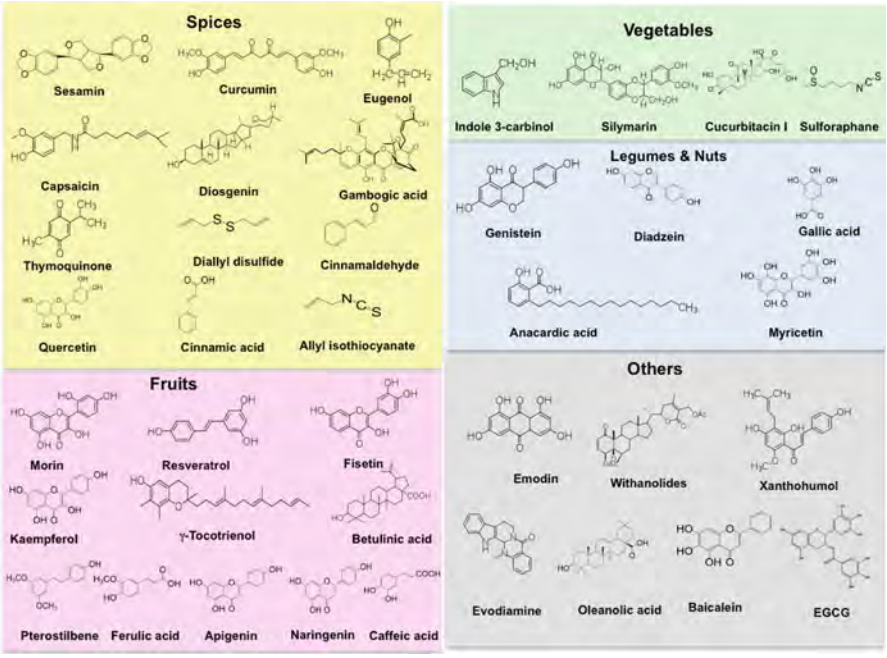

Fig. 9.2 Structure of natural compounds involved in regulation of the ubiquitin proteasome degradation pathway

various tumors (Aggarwal et al. 2007). Curcumin-responsive cells were also found to accumulate poly-ubiquitinated proteins and cyclin B, which results in disturbance of the ubiquitin-proteasome system and cell cycle arrest (O'Sullivan-Coyne et al. 2009).

Further mechanistic study showed that curcumin behaves like proteasome. The nucleophilic susceptibility and in silico docking studies have revealed that both carbonyl carbons of the curcumin molecule are susceptible to a nucleophilic attack by the hydroxyl group of the NH2-terminal threonine of the proteasome CTL subunit. It was confirmed in a biological system that curcumin potently inhibits the CTL activity of purified rabbit 20S and cellular 26S proteasomes and inhibits proteasome activity in human colon cancer cell lines, leading to accumulation of ubiquitinated proteins and several proteasome target proteins, and subsequent induction of apoptosis. Furthermore, in a xenograft colorectal imprinting control region severe combined immunodeficiency (ICR SCID) mice model, curcumin resulted in decreased tumor growth, associated with proteasome inhibition, proliferation suppression, and apoptosis induction in tumor tissues, indicating the mechanisms by which curcumin plays its chemopreventive and therapeutic roles (Milacic et al. 2008).

Other studies have shown that the apoptosis induction by spices was associated with disruption of ubiquitin proteasome system function by directly inhibiting the

Table 9.1 Cell signaling targets downregulated by natural compounds through modulation of proteasome pathway

Targets	References
Spices	
Curcumin	
ARNT	Choi (2006)
Bcl-2	Chanvorachote (2009)
COP9 signalosome	Henke (1999)
COX-2	Neuss (2007)
Cyclin D1	Srivastava (2007)
Cyclin E	Srivastava (2007)
hTERT	Lee (2010)
Id1 and Id3	Berse (2004)
iNOS	Ben (2011)
p38	Poylin (2008)
p300	Marcu (2006)
Sp1	Hsin (2010)
Sesamin	
Cyclin D1	Yokota (2007)
Quercetin	
FLIP	Kim (2008)
HER2/neu	Jeong (2008)
Mcl-1	Spagnuolo (2011)
Ras	Psahoulia (2007)
Survivin	Siegelin (2009)
Fruits and vegetables	
Silybinin	
FLIP	Son (2007)
Survivin	Son (2007)
AR	Deep (2008)
Sulforaphane	
AR	Gibbs (2009)
ER	Ramirez (2009)
Bim-1, H3K27me3, Ezh2	Balasubramanian (2011)
Nrf2	McMahon (2003)
Resveratrol	
Aβ	Marambaud (2005)
Cyclin D1	Joe (2002)
ER	Pozo-Guisado (2004)
HIF-1α	Zhang (2005)
Id1 and Id3	Berse (2004)
Tubocapsenolide A	
Akt, Cdk4	Chen (2008)
CDDO-Me	
FLIP	Zou (2007)
γ-Tocotrienol	
Apolipoprotein B	Wang (1998)
Apigenin	
HER2/neu	Way (2004)

(continued)

Table 9.1 (continued)

Targets	References
Ferulic acid	
MMP-2/MMP-9	Staniforth (2012)
Betulinic acid	
Sp proteins	Chintharlapalli (2007)
Legumes and nuts	
Anacardic acid	
Histone acetylation	Song (2010)
CDDO	
c-FLIP	Zou (2007)
Genistein	
GR	Kinyamu (2003)
Top2β	Azarova (2010)
AR	Basak (2008)
HER2/neu	Magnifico (1998)
c-FLIP	Siegelin (2009)
Others	
Withaferin A	
AR	Yang (2007)
NF-κB	Mohan (2004)
EGCG	
Bad, p27, IκBα	Smith (2002), Nam (2001)
bFGF	Sukhthankar (2008)
VEGF	Konta (2010)
PcG proteins	Choudhury (2011)
P38 MAPK	Kazi (2002)
Emodin	
Id1 and Id3	Berse (2004)
AR	Cha (2005)
ERα	Zhang (2011)
Withanolide	
ER	Zhang (2011)
Gambogic acid	
Mutant p53	Wang (2011)
ABCB1	Wang (2012)
MDM2	Rong (2009)
P53	Wang (2012)

ABCB1 ATP-binding cassette transporter B1, *ABCB1* ATP-binding cassette transporter B1, *Aβ* amyloid-beta, *AR* androgen receptor, *ARNT* aryl hydrocarbon receptor nuclear translocator, *Bcl-2* B-cell lymphoma 2, *bFGF* basic fibroblast growth factor, *CDDO-Me* methyl-2-cyano-3 12-dioxooleana-1 9-dien-28-oate, *Cdk4* cyclin-dependent kinase 4, *COP9* signalosome photomorphogenic 9 signalosome, *COX-2* cyclooxygenase-2, *EGCG* epigallocatechin gallate, *ER* estrogen receptor, *Ezh2* enhancer of zeste homolog 2, *FLIP* Fas-associated death domain-like interleukin-1beta-converting enzyme (FLICE)-like inhibitory protein, *GR* glucocorticoid receptor, *H3K27me3* trimethylated lysine 27 of histone 3, *HIF-1α* hypoxia inducible factor-1alpha, *hTERT* human telomerase reverse transcriptase, *Id1* inhibitor of DNA binding 1, *iNOS* inducible NO synthase, *MAPK* mitogen-activated protein kinase, *Mcl-1* myeloid cell leukemia sequence 1, *MDM2* murine double minute 2, *MMP-2* matrix metalloproteinase-2, *Nrf2* nuclear factor-erythroid 2-related factor 2, *PcG* polycomb group, *Sp1* specificity protein 1, *Top2* topoisomerase II , *VEGF* vascular endothelial growth factor

Table 9.2 Cell signaling targets upregulated by natural compounds through modulation of proteasome pathway

Targets	Natural compounds	References
Spices		
Bax	Capsaicin, thymoquinone	Maity (2010), Cecarini (2010)
HDAC2	Curcumin	Meja (2008)
HIF-1α	Quercetin	Lee (2008)
HIF-2α	Quercetin	Park (2008)
IκBα	Curcumin, capsaicin	Dikshit (2006a, b), Mori (2006)
Nrf2	Quercetin	Tanigawa (2007)
NS2	Curcumin	Franck (2005)
P21	Curcumin	Aggarwal (2007)
P27	Capsaicin	Maity (2010)
P53	Curcumin, capsaicin, thymoquinone	Bech-Otschir (2001), Maity (2010), Cecarini (2010)
XBP1	Quercetin	Klappan (2012)
Fruits and vegetables		
IκBα	Cucurbitacin D, resveratrol, genistein, withanolide D	Ding (2011), Shakibaei (2008), Kazi (2003), Bargagna-Mohan (2006)
P27	Genistein	Kazi (2003)
Legumes and nuts		
p21(Kip1), p53, CHOP	CDDO, GA	Lapillonne (2003), Rong et al. (2009)
Others		
p27(Kip1), p53	Tocopherol	Munteanu (2007)
IκBα, Bax, p27	Withaferin A	Yang (2007)

CHOP CAAT/enhancer binding protein, *GA* gambogic acid, *HDAC2* human histone deacetylase 2, *HIF-1α* hypoxia inducible factor-1alpha, *HO-1* heme oxygenase-1, *Nrf2* nuclear factor-erythroid 2-related factor 2, *NS2* nonstructural 2, *XBP1* X-box binding protein 1

enzyme activity of the proteasome's 20S core catalytic component. Like other proteasome inhibitors, curcumin exposure induces neurite outgrowth and the stress response, as evidenced by the induction of various cytosolic and ER chaperones as well as induction of transcription factor CHOP/GADD153 (Dikshit et al. 2006a). Curcumin has also been shown to inhibit the ubiquitin isopeptidase activity and cause cell death independent of p53 in isogenic pairs of RKO and HCT116 cells (Mullally and Fitzpatrick 2002). Inhibition of isopeptidase activity by curcumin leads to the accumulation of ubiquitin-protein conjugates and polyubiquitin because of the lack of ubiquitin recycling. Excessive accumulation of ubiquitin-protein conjugates could conceivably create proteasome dysfunction. It has been reported that curcumin exhibits anticancer activity in cell lines and the hepatoma xenograft model through inhibition of hypoxia-inducible factor (HIF)-1 activity and downregulation of its targeted genes. Moreover, of the two HIF-1 subunits, only aryl hydrocarbon receptor nuclear translocator (ARNT) was found to be repressed

by curcumin in cancer cells. The repression of ARNT by curcumin was stimulated by the proteasome degradation *via* oxidation and ubiquitination processes (Choi et al. 2006). Curcumin also inhibited telomerase activity and accumulated human telomerase reverse transcriptase (hTERT) in the cytoplasmic compartment of the cell. The curcumin-induced cytoplasmic retention of hTERT protein resulted in rapid ubiquitination and degradation by the proteasome (Lee and Chung 2010). Specificity protein 1 (Sp1), one of the more important transcription factors in hTERT expression, is also inhibited through the proteasome pathway in A549 cells (Hsin et al. 2010).

An important regulator of the ubiquitin proteasome system is the COP9 signalosome (CSN), which controls the stability of many proteins. Curcumin significantly induces ubiquitination and proteasome-dependent degradation of transcriptional regulators and substrates of the ubiquitin system inhibitor of DNA binding (Id) 1 and Id3 in HeLa cells. Id2 and Id4 bind to CSN subunit CSN5 and regulate the ubiquitination by specific ubiquitin ligases (Berse et al. 2004). The CSN, a kinase complex, cooperates with the ubiquitin/26S proteasome system in regulating the stability of proteins involved in signal transduction. The components of CSN possess homologies with eight non-ATPase regulatory subunits of the 26S proteasome. Curcumin has been shown to be a potent inhibitor of the CSN kinase activity with a Ki of about 10 μM (Henke et al. 1999). Because of this, curcumin blocks E6-dependent p53 degradation in reticulocyte lysates as CSN targets human p53 to ubiquitin-26S proteasome-dependent degradation (Bech-Otschir et al. 2001). As an inhibitor of CSN-associated kinases, curcumin also showed proteasome-dependent degradation of cyclooxygenase-2 (COX-2) in HeLa cell lysate and in HeLa cells (Neuss et al. 2007).

Curcumin can overcome cisplatin resistance in cancer cells. For instance, co-treatment of the cells with curcumin and cisplatin resulted in increased apoptosis and reversal of Bcl-2-mediated cisplatin resistance. The mechanism by which curcumin downregulates Bcl-2 and sensitizes cells to cisplatin-induced apoptosis involves proteasome degradation of Bcl-2 (Chanvorachote et al. 2009). This ubiquitin-proteasome degradation of Bcl-2 by curcumin also sensitizes non-small cell lung cancer cell anoikis and detachment-induced apoptosis (Pongrakhananon et al. 2010). In the *Xenopus laevis* (frog) model system, curcumin inhibited proteasome activity and induced the accumulation of heat shock proteins (HSPs) at the transcriptional level. It has been found that the treatment of A6 kidney epithelial cells with curcumin enhanced ubiquitinated protein levels and inhibited CTL activity (Khan and Heikkila 2011). Besides these effects, curcumin promoted proteasome-dependent degradation of p300 and the closely related CREB binding protein (CBP). In addition to inducing p300 degradation, curcumin inhibited the acetyltransferase activity of purified p300 as assessed by using either histone H3 or p53 as substrate (Marcu et al. 2006).

The direct inhibition of proteasome activity also causes an increase in the half-life of IκB α that ultimately leads to the downregulation of NF-κB activation (Dikshit et al. 2006b). Another report suggested that curcumin did not affect phosphorylation of IκB α, although it significantly inhibited proteasomal activity in MCF-7 cells.

It has the capability of inhibiting tumor necrosis factor (TNF)-α-induced NF-κB activation of MCF-7 cells by inhibiting the proteasome activities instead of inhibiting IκB kinase (IKK) activation (Yoon and Liu 2007). Another study reported that curcumin at nanomolar concentrations specifically restores cigarette smoke extract- or oxidative stress-impaired histone deacetylase 2 (HDAC2) activity. Biochemical and gene chip analysis indicated that curcumin at concentrations up to 1 μM propagates its effect *via* antioxidant-independent mechanisms associated with the phosphorylation-ubiquitin-proteasome pathway. It reversed HDAC2 protein expression even in the presence of the protein synthesis inhibitor cycloheximide, which indicates that curcumin acts at a post-translational level by maintaining both HDAC2 activity and expression (Meja et al. 2008). Curcumin has also been shown to promote the ubiquitination and degradation of inducible nitric oxide (NO) synthase (iNOS) after lipopolysaccharide (LPS) stimulation. In LPS-stimulated murine macrophage-like RAW 264.7 cells, curcumin induced the degradation of iNOS protein through ubiquitination and proteasome mechanisms (Ben et al. 2011).

As a proteasome inhibitor, curcumin has been shown to be useful for the treatment of muscle wasting in cancer cachexia. In one study, curcumin completely attenuated proteolysis-inducing factor (PIF)-induced total protein degradation in murine myotubes, and also attenuated the PIF-induced increase in the expression of the ubiquitin-proteasome proteolytic pathway, as determined by the CTL enzyme activity, proteasome subunits and $E2_{14k}$ (Wyke et al. 2004). Another study showed that curcumin influenced proteolytic pathways that are activated in septic muscle, including ubiquitin-proteasome-dependent proteolysis. In a rat model, curcumin treatment prevented a sepsis-induced increase in muscle protein breakdown. It has also been observed that the upregulated expression of the ubiquitin ligases atrogin-1 and MuRF1 was not influenced by curcumin. When muscles from septic rats were treated with curcumin *in vitro*, proteasome-dependent protein breakdown rates were reduced, and nuclear NF-κB activity and activated p38 were decreased, which suggests that sepsis-induced muscle proteolysis can be blocked by curcumin (Poylin et al. 2008). Curcumin also regulates the proteasome degradation of short-lived protein hepatitis C virus nonstructural 2, which is described to be involved in apoptosis inhibition and gene transcription modulation. Curcumin mediates inhibition of casein kinase 2 activity, which leads to suppression of nonstructural 2 phosphorylation and proteasome degradation and, subsequently, stabilized expression *in vitro* (Franck et al. 2005). In polyglutamine diseases, curcumin promotes mutant huntingtin-induced cell death by mimicking proteasome dysfunction. The treatment of curcumin increases the polyglutamine-expanded truncated N-terminal huntingtin (mutant huntingtin) aggregation and mutant huntingtin-dependent cell death. Curcumin also causes rapid proteasome malfunction in the mutant huntingtin-expressing cells in comparison with normal glutamine repeat expressing cells (Dikshit et al. 2006b).

Flavonoids have also been shown to exhibit chemopreventive and chemotherapeutic activities by modulating the proteasome pathway. Quercetin, one of the flavonoids present in a variety of fruits, vegetables, nuts, and spices, inhibits the ubiquitination of HIF-1/2α in normoxia by hindering HIF-1/2α proline

hydroxylase through chelating iron ions (Park et al. 2008). Quercetin also enhanced the antioxidant response element binding activity and NF-E2-related factor 2 (Nrf2)-mediated transcriptional activity as studied in human HepG2 cells. Molecular evidence revealed that quercetin not only upregulated the expression of Nrf2 mRNA and protein, but also stabilized Nrf2 protein by inhibiting the ubiquitination and proteasome turnover of Nrf2 (Tanigawa et al. 2007). In addition, quercetin induced ubiquitination of HER2/neu in which the carboxyl terminus of Hsc70-interacting protein, a chaperone-dependent E3 ubiquitin ligase played a crucial role (Jeong et al. 2008). Treatment with quercetin significantly decreased the protein levels of c-FLIP, an inhibitor of caspase-8, through proteasome-mediated degradation and recovers TNF-related apoptosis-inducing ligand (TRAIL), sensitivity in various human hepatocellular carcinoma cells (Kim et al. 2008). Quercetin exposure also resulted in proteasome degradation of survivin and enhanced death-receptor-mediated apoptosis in glioma cells (Siegelin et al. 2009).

Angioprotective properties of quercetin have been also reported, which is mediated by proteasome proteolysis. It has the ability to modulate proteasome activity in a rabbit model of cholesterol-induced atherosclerosis. A single intravenous injection of the water-soluble form of quercetin (Corvitin) significantly decreased proteasome TL activity 1.85-fold in monocytes, and decreased the CTL and peptidyl-glutamyl peptide-hydrolyzing (PGPH) activities more than two-fold in polymorphonuclear leukocytes. Prolonged administration of Corvitin to animals following a cholesterol-rich diet significantly decreased all types of proteolytic proteasome activities both in tissues and in circulating leukocytes and has been shown to be associated with the reduction of atherosclerotic lesions in the aorta (Pashevin et al. 2011). In other study, quercetin and its derivative quercetin caprylate were identified as a proteasome activator with antioxidant properties that consequently influence the cellular lifespan, survival, and viability of HFL-1 primary human fibroblasts. Moreover, when these compounds are supplemented to already senescent fibroblasts, a rejuvenating effect is observed (Chondrogianni et al. 2010). In human HaCaT keratinocytes, quercetin enhanced arsenic-induced apoptosis. A decrease in the p53 protein with increased protein ubiquitination was detected in quercetin/As(+3)-treated HaCaT cells. The decrease in the p53 protein by quercetin/As(+3) was reversed by adding the proteasome inhibitor, MG132 (Shen et al. 2012).

Several other flavonoids (including apigenin-6-hydroxy-7-*O*-beta-*D*-glucoside, rutin, 6-hydroxyapigenin, 5,6,4′-trihydroxy-7,3′-dimethoxyflavone, 5,6,3′,4′-tetrahydroxy-7-methoxyflavone, glycitecin, and 6,7,4′-trihydroxyisoflavone) also inhibit CTL caspase-like or TL activity of 26S proteasome in pig red blood cells (Chang 2009). Another study showed that apigenin and quercetin are much more potent than kaempferol and myricetin in inhibiting CTL activity of purified 20S proteasome and of 26S proteasome in intact leukemia Jurkat T cells as well as in accumulating putative ubiquitinated forms of two proteasome target proteins, Bax and IκBα, in Jurkat T cells (Chen et al. 2005).

Sesamin, a component of sesame seeds, has shown anticancer effects in different human cancer cells mediated through the ubiquitin proteasome pathway. It inhibits

proliferation of cancer cells *via* downregulation of cyclin D1 in various kinds of human tumor cells, including lung cancer, transformed renal cells, immortalized keratinocyte, melanoma, and osteosarcoma by promoting proteasome degradation of the cyclin D1 protein (Yokota et al. 2007). Thymoquinone, another spice nutraceutical present in *Nigella sativa* (black cumin), induces selective proteasome inhibition, both in isolated enzymes and in glioblastoma cells, which leads to the induction of apoptosis in cancer cells. In one study, U87 MG and T98G malignant glioma cells were treated with thymoquinone, an inhibition of 20S and 26S; proteasome activity was observed in both cell lines, accompanied by the accumulation of ubiquitin conjugates. The accumulation of p53 and Bax, two proteasome substrates with proapoptotic activity, was also observed in both cell lines (Cecarini et al. 2010), indicating thymoquinone's proteasome inhibitory properties.

Cinnamate esters, present in the bark of cinnamon, are reported to be an inhibitor of proteasome activity while cinnamic acid amides had no inhibitory activity against proteasomes (Arbiser et al. 2005). Another study on the garlic component diallyl sulfide showed that it prevented the decreased proteasome peptidase activities in ethanol-exposed VL-17A cells (Osna et al. 2007), suggesting its proteasome modulating properties. Capsaicin, a spice component of chili, induced apoptosis of mouse neuro 2a cells *via* the inhibition cellular proteasome function. Exposure of capsaicin in this mouse neuro 2a cells causes increased oxidative stress and the accumulation of ubiquitinated proteins, as well as various target substrates of proteasomes such as p53, Bax and p27 (Maity et al. 2010). However, capsaicin induced the degradation of tumor suppressor p53, which is blocked by the proteasome inhibitor MG132, and enhanced apoptotic cell death in the human breast cell line MCF10A (Lee et al. 2009). Moreover, capsaicin inhibited TNF-α-stimulated degradation of IκBα through inhibiting proteasome activity and preventing the activation of NF-κB in PC-3 cells. This could be the probable mechanism of capsaicin-induced decrease of prostate tumor growth in a xenograft mouse model (Mori et al. 2006).

9.4.2 Fruits and Vegetables

Fruits and vegetables are considered the most important source of nutraceuticals. Indole-3-carbinol and its dimeric product 3,3′-diindolylmethane (DIM), components of cruciferous vegetables, inhibit prostate cancer cell growth and induce apoptosis. The anticancer effects of DIM were linked to the proteasome mechanism. DIM inhibited proteasome activity in the S phase, which led to the inactivation of NF-κB signaling and the induction of apoptosis in LNCaP and C4-2B cells (Chinnakannu et al. 2009). The inactivation of NF-κB was also achieved with cucurbitacin. Treating T cell leukemia cells with cucurbitacin D induced inhibition of proteasome degradation of IκBα, which resulted in its accumulation, and suppression of NF-κB activation (Ding et al. 2011). Caffeic acid, which occurs naturally in many agricultural products

such as fruits, vegetables, wine, olive oil, and coffee, induced the inhibition of NF-κB, which is associated with the proteasome pathway (Thornton et al. 2010).

Isosilybin B, a component of milk thistle, exhibited anticancer effects in human prostate cancer cells. Treatment of isosilybin B in prostate cancer cells enhances the formation of a complex between Akt, Mdm2, and androgen receptor (AR), which promotes phosphorylation-dependent AR ubiquitination and its degradation by proteasome (Deep et al. 2008). Another component of milk thistle, silibinin, downregulated antiapoptotic proteins FLIP(L), FLIP(S), and survivin through proteasome-mediated degradation. This activity of silibinin modulates multiple components in the death receptor-mediated apoptotic pathway and recovered TRAIL sensitivity in TRAIL-resistant glioma cells (Son et al. 2007).

The flavonoids, such as isothiocyanates, which include benzyl isothiocyanate, phenethyl isothiocyanate and sulforaphane, found in cruciferous vegetables, are highly effective in inducing cell cycle arrest and apoptosis in a variety of cancer cells and animal models through inhibition of the proteasome pathway. Dietary isothiocyanate has been shown to suppress cancer progression by reducing the polycomb group (PcG), which is present at elevated levels in cancer cells, *via* a proteasome-dependent mechanism, thereby inhibiting PcG-dependent pro-survival epigenetic events. It also induced proteasome-dependent degradation of both alpha- and beta-tubulins in a variety of human cancer cell lines (Mi et al. 2009). Benzyl isothiocyanate and phenethyl isothiocyanate significantly inhibited both the 26S and 20S proteasomes, presumably through direct binding in a variety of cell types. The potency of isothiocyanate-induced proteasome inhibition correlates with the rapid accumulation of p53 and IκBα, demonstrating that benzyl isothiocyanate and phenethyl isothiocyanate are the strongest proteasome inhibitors causing cell cycle arrest and apoptosis (Mi et al. 2011).

Sulforaphane induced a concentration-dependent proteasome degradation of PcG protein (Bmi-1, Ezh2) in SCC-13 skin cancer cells and also reduced trimethylation of lysine 27 of histone H3. This is associated with accumulation of cells in G2/M phase; reduced levels of cyclin B1, cyclin A, cyclin dependent kinases (CDK) 1 and 2; and increased p21(Cip1) expression (Balasubramanian et al. 2011). It has also been shown to enhance proteasome activities in mammalian cells and to reduce the level of oxidized proteins and amyloid β-induced cytotoxicity in murine neuroblastoma Neuro2A and N1E 115 cells (Park et al. 2009). Further mechanistic studies revealed that sulforaphane enhances the expression of the catalytic subunits of the proteasome, as well as proteasome peptidase activities. Depending on the upregulation of the proteasome system it acts as cytoprotective agent against hydrogen peroxide-mediated cytotoxicity (Kwak et al. 2007). Another study showed that sulforaphane induced expression of HSP27 through the stimulation of proteasome activity (Gan et al. 2010). In prostate cancer cells, sulforaphane induced the hyperacetylation of HSP90, which in turn destabilizes AR and promotes further proteasome degradation (Gibbs et al. 2009). In breast cancer MCF-7 cells, sulforaphane inhibited the expression of estrogen receptor (ER)α protein in part at the transcriptional level as well as increased proteasome-mediated degradation (Ramirez and Singletary 2009).

Sulforaphane has also been shown to inhibit Keap1-dependent ubiquitination of PGAM5 as a novel substrate for Keap1 (Lo and Hannink 2006). Keap1 is a negative regulator of Nrf2, a bZIP transcription factor that mediates adaptation to oxidative stress. In the RL34 non-transformed rat liver cell line, Nrf2 was found to accumulate rapidly in response to oxidative stress caused by treatment with sulforaphane, and the accumulation resulted from inhibition of proteasome-mediated degradation of the bZIP protein (McMahon et al. 2003). Sulforaphane increases the expression of genes through the Nrf2 signaling pathway that directly detoxify exogenous toxins/carcinogens or endogenous reactive oxygen species, as well as genes involved in the recognition and repair/removal of damaged proteins, which possibly provide secondary protection against DNA or protein damage, enhancing cell survival (Hu et al. 2006).

Resveratrol, pterostilbene, and morin hydrate caused significant inhibition in the activities of CTL, TL, and post-acidic (post-glutamase) proteasome sites in RAW 264.7 cells. Consequently, it inhibits NF-κB activation by the proteasome and suppresses activation of pro-inflammatory cytokines and iNOS genes, resulting in decreased secretion of TNF-α, interleukin (IL)-1β, IL-6, and NO levels, in response to inflammatory stimuli (Qureshi et al. 2012). Another study showed that resveratrol, like N-Ac-Leu-Leu-norleucinal (ALLN), suppressed IL-1beta-induced NF-κB activation through the inhibition of proteasome function and the degradation of IκBα without affecting IKK activation, IκBα-phosphorylation or IκBα-ubiquitination. Resveratrol and ALLN also inhibited IL-1β-induced apoptosis, caspase-3 activation, and poly (ADP-ribose) polymerase cleavage in human articular chondrocytes (Shakibaei et al. 2008). The inhibition of NF-κB activation through the ubiquitin-proteasome pathway by resveratrol was also shown to be effective in the preservation of skeletal muscle mass in cachexia to prevent muscle wasting (Tisdale 2005).

Resveratrol has been reported to increase the expression levels of heme oxygenase (HO)-1 protein through the activation of PI3K/Akt pathway. The induction of HO-1 protein was found to be associated with inhibition of the ubiquitination-dependent proteasome pathway, which in turn melatonin (a neurohormone) potentiates the neuroprotective effect of resveratrol against oxidative injury (Kwon et al. 2011). In Alzheimer's disease, resveratrol has shown proteasome-dependent anti-amyloidogenic activity. Although resveratrol does not inhibit Abeta production, it promotes intracellular degradation of Abeta *via* a mechanism that involves the proteasome (Marambaud et al. 2005). It has also been reported that resveratrol triggers ER stress and cell death in dopaminergic N27 cells through caspase activation, p23 cleavage, and inhibition of proteasome activity in dopaminergic N27 cells (Chinta et al. 2009). Resveratrol also has the potential to negate the cytotoxic effects of proteasome inhibitors *via* regulation of forkhead box protein O1 (FOXO1) transcriptional activity and accumulation of p27Kip1 (Niu et al. 2011).

Resveratrol modulates peroxisome proliferator-activated receptor (PPAR) γ protein levels in 3T3-L1 adipocytes *via* inhibition of PPARgamma gene expression coupled with increased ubiquitin-proteasome-dependent degradation (Floyd et al.

2008). It also inhibits hypoxia-induced HIF-1α accumulation by enhanced protein degradation through the 26S proteasome system (Zhang et al. 2005). Proteasome-dependent degradation of the ERα was also observed in breast cancer MCF-7 cells, which caused inhibition of cell proliferation and induction of apoptosis (Pozo-Guisado et al. 2004).

Fisetin blocks mitosis in a proteasome-dependent manner in several human cell lines. The inhibition of mitosis by fisetin was mediated through targeting Aurora B kinase, which contributes its antiproliferative effects (Salmela et al. 2009). However, fisetin has also been shown to promote nerve cell survival by increased proteasome activity (Maher 2008). Other flavonoids such as luteolin, apigenin, chrysin, naringenin, and eriodictyol also inhibit proteasomes. The order of inhibitory potencies of 20S purified proteasome was luteolin > apigenin > chrysin (Chen et al. 2007). It has been reported that methanol extract of the stems of *Spatholobus suberectus*, which contain liquiritigenin, isoliquiritigenin, genistein, daidzein, medicarpin, 7-hydroxyflavanone, and formononetin, inhibit 20S proteasomes (Shim 2011). Apigenin inhibits the proteasome CTL activity and induces apoptosis not only in cultured MDA-MB-231 cells but also in MDA-MB-231 xenografts (Chen et al. 2007). Apigenin dissociated the complex of HER2/neu and GRP94 that preceded the depletion of HER2/neu. Apigenin-induced degradation of mature HER2/neu involves polyubiquitination of HER2/neu and subsequent hydrolysis by the proteasome in breast cancer cells (Way et al. 2004).

Ferulic acid suppresses matrix metalloproteinase (MMP)-2 and MMP-9 mediated *via* the proteasome pathway in ultraviolet B-irradiated mouse skin tissues (Staniforth et al. 2012). Kaempferol treatment resulted in proteasome degradation of survivin, which was involved in kaempferol-mediated TRAIL-induced apoptosis (Siegelin et al. 2008). Betulinic acid (BA) induces proteasome-dependent degradation of transcription factors specificity protein (Sp) 1, Sp3, and Sp4 in prostate cancer cells and induced antiangiogenic and proapoptotic activities (Chintharlapalli et al. 2007). It is also reported as a potent proteasome activator that preferentially activates the CTL activity of the proteasome. Chemical modifications at the C-3 position of BA (dimethylsuccinyl BA) converted it to proteasome inhibitors with various biological activities against the human 20S proteasome (Huang et al. 2007).

Beta-carotene, which is extensively present in carrots, dark-green leafy vegetables, including spinach and green leaf lettuce, sweet potatoes and broccoli, exhibits anti-cancer and anti-inflammatory properties through modulation of proteasome pathway. The carotene breakdown products modify tau and ferritin proteins and such modifications enhanced their proteasomal degradation through recognition of 20S proteasome subunit (Sommerburg et al. 2009). Omega-3 fatty acid, another dietary compound appeared to accelerate AR protein degradation, which was blocked by proteasome inhibitor MG132 indicating its degradation is mediated through proteasome pathway (Wang et al. 2012). Knockdown of AR significantly slowed down prostate cancer cell proliferation in the absence of androgens.

Vitamins are fond be major regulator of gene expression in higher organisms. Vitamin D and its metabolite 1α,25-dihydroxyvitamin D(3), has shown to modulate the function of the ubiquitin-proteasome system (Alvarez-Diaz et al. 2010).

Another study showed that proteasome inhibitor enhanced 1,25(OH)(2)D(3)-induced CYP24A1 expression and nuclear vitamin D receptor (VDR) expression indicating 1,25(OH)(2)D(3) induced their expression through ubiquitin-proteasome pathway (Amano et al. 2009). However, numerous studies have shown that ascorbic acid (vitamin C) inhibits bortezomib-induced cytotoxicity against endometrial carcinoma cells (Llobet et al. 2008), multiple myeloma (Perrone et al. 2009) and several other cancer cells (Zou et al. 2006) *in vitro*. It has been shown *in vitro* multiple myeloma cells that vitamin c blocks bortezomib-induced inhibitory effect on 20S proteasome activity. Even *in vivo* study on xenograft model of human multiple myeloma in SCID (severe combined immune-deficient) mice evident that oral intake of vitamin C (40 mg/kg/day) significantly blocks bortezomib-induced inhibition of tumor growth (Perrone et al. 2009).

9.4.3 Legumes and Nuts

Legumes and nuts contain a variety of phytochemicals. These phytochemicals act as chemopreventive and therapeutic agents in several ways, including the proteasome-signaling pathway. Genistein is one of the natural phytochemicals, induced proteasome degradation of topoisomerase II (Top2)β in 32Dc13 cells. It efficiently induced both Top2α and Top2β cleavage complexes in the purified system and in cultured mouse cells, which play a major role in infant leukemia (Azarova et al. 2010). The anacardic acid has been shown to attenuate histone acetylation, as pesticide dieldrin induces acetylation of core histones because of proteasome dysfunction and this hyperacetylation plays a key role in dopaminergic neuronal degeneration (Song et al. 2010).

Treatment of genistein to LNCaP cells exhibited increased ubiquitination of AR, suggesting that AR protein is downregulated *via* a proteasome-mediated pathway in prostate cancer cells. The increased ubiquitination of AR after genistein treatment was associated with a decrease in Hsp90 chaperone activity (Basak et al. 2008). Genistein also enhanced proteasome degradation of the short isoform of c-FLIP and thus facilitated TRAIL-mediated apoptosis in malignant glioma cells (Siegelin et al. 2009). CDDO-Me, an analogue of oleanoic acid, induced ubiquitin/proteasome-dependent c-FLIP degradation. This c-FLIP downregulation contributes to CDDO-Me-initiated apoptosis and enhancement of TRAIL-induced apoptosis (Zou et al. 2007). Another analogue of oleanoic acid, CDDO-Im, either alone or in combination with bortezomib, has been shown to overcome drug resistance in multiple myeloma patients (Chauhan et al. 2004). CDDO also upregulates proteins involved in the ubiquitin-proteasome pathway and p21 (Waf1/CIP1), GADD153, and CAAT/enhancer binding protein transcription factor family members in breast cancer MCF-7 and MDA-MB-435 cells (Lapillonne et al. 2003).

9.4.4 Others

Other natural compounds such as tocotrienol, found in palm oil, rice, and barley, inhibits inflammatory responses by inhibiting activation and nuclear translocation NF-κB through inhibition of proteasome-mediated IκBα degradation (Qureshi et al. 2011). Further mechanistic study showed that α-, γ-, or δ-tocotrienol inhibited the CTL activity of 20S as shown in rabbit muscle proteasomes (Qureshi et al. 2010). Tocotrienol has been shown to modulate differential interaction of mitogen-activated protein (MAP) kinases with caveolin 1/3 in conjuncture with proteasome stabilization, which plays a unique role in tocotrienol-mediated cardioprotection (Das et al. 2008). Other than α-tocotrienol, γ-tocopherol and α-tocopheryl phosphate also inhibited cellular proteasome activity and increased the level of p27 (Kip1) and p53 in THP-1 monocytes (Munteanu et al. 2007).

Emodin (from *Rheum emodi*, a Himalayan rhubarb, buckthorn, and Japanese knotweed) inhibits CSN-associated kinases and significantly induces ubiquitination and proteasome-dependent degradation of transiently expressed Id3 in HeLa cells. Proteasome-dependent degradation of endogenous Id1 in HeLa cells was also stimulated by emodin (Berse et al. 2004). In T cell lymphomas, emodin accelerates c-myc protein turnover in a proteasome-dependent manner (Channavajhala and Seldin 2002). Emodin decreased the association of AR and HSP90 and increased the association of AR and MDM2, which in turn induces AR degradation through the proteasome-mediated pathway in prostate cancer cells and thus exhibits anti-cancer effect (Cha et al. 2005).

In breast cancer cells, withaferin A, a natural compound from the ayurvedic plant (Chitrak), downregulates the ERα protein levels by proteasome-dependent ERα degradation (Zhang et al. 2011). Withaferin A also inhibits inflammation in various cancer cells by inhibiting NF-κB activation through the proteasome pathway. The inhibition of NF-κB in HUVECs by withaferin A occurs by interference with the ubiquitin-mediated proteasome pathway as it increases the levels of poly-ubiquitinated proteins (Mohan et al. 2004). In prostate tumor cells, it accumulates ubiquitinated proteins and the IκBα, Bax, and p27 proteasome targets which results in degradation of the AR protein in androgen-dependent LNCaP cells and apoptosis induction. Furthermore, withaferin A potently inhibits the CTL activity of purified rabbit 20S and 26S proteasomes in human prostate cancer cultures and xenografts. Further computational modeling studies predict that C1 and C24 of withaferin A are highly susceptible for a nucleophilic attack by the hydroxyl group of N-terminal threonine of the proteasome chymotrypsin subunit β5 (Yang et al. 2007). In addition, docking studies carried out with herbal ligand withaferin A in the structures of bovine and human proteasomes substantiate that it has the ability to inhibit activity of mammalian 20S proteasomes by blocking the nucleophilic function of N-terminal Thr1 (Grover et al. 2010).

Xanthohumol, another natural compound from hops, showed proteasome inhibitory activity and induced apoptosis of chronic lymphocytic leukemia cells (Lust et al. 2009). Evodiamine induces A375-S2 cell death through the PI3K/Akt/caspase and

Fas-L/NF-κB signaling pathways, and these signals have been shown to be augmented by the ubiquitin-proteasome pathway (Wang et al. 2010). Another natural compound, baicalein, exhibits cytoprotective activity against 6-hydroxydopamine-induced oxidative injury, which was attenuated by the proteasome inhibitor MG132 (Jiang et al. 2012), which indicates that the cytoprotective effect of baicalein was mediated through the proteasome pathway.

Black tea extract enriched in theaflavins inhibited the CTL activity of the proteasome and the proliferation of human multiple myeloma cells. An isolated theaflavin can bind to and inhibit the purified 20S proteasome, accompanied by suppression of tumor cell proliferation (Mujtaba and Dou 2012). Epigallocatechin gallate (EGCG), a component of green tea, also has been shown to be potent and specifically inhibits the CTL activity of purified 20S proteasome and the 26S proteasome in tumor cell lysates. Treatment of leukemic Jurkat T or prostate cancer LNCaP cells with EGCG accumulated p27 and IκBα proteins, which further resulted in cell cycle arrest and apoptosis by accumulation of the Bad protein (Nam et al. 2001; Smith et al. 2002). Sukhthankar et al. (2008) showed that EGCG increases the ubiquitination of basic fibroblast growth factor (bFGF) and TL activity of the 20S proteasome, resulting in the degradation of the bFGF protein. Combining tea polyphenols with gallic acid inhibited 20S proteasomes with gradual inhibition of CTL, TL, PGPH and BrAAP (Amici et al. 2008). It has been shown that analogues of (−)-EGCG containing a para-amino group on the D-ring in place of the hydroxyl groups have proteasome inhibitory activities (Osanai et al. 2007). However, its methylation decreases proteasome-inhibitory activity, contributing to decreased cancer-preventive effects of tea consumption (Landis-Piwowar et al. 2007).

Both tyrosinase and vascular endothelial growth factor (VEGF) protein levels have been shown to be remarkably reduced during EGCG treatment. Further, the hindrance of tyrosinase and VEGF protein synthesis could be prevented by the use of the proteasome inhibitor lactacystine, indicating that EGCG-induced degradation of these proteins was mediated by the proteasome pathway (Konta et al. 2010). Another study showed that the EGCG-induced reduction in PcG protein level is associated with increased ubiquitination and is reversed by proteasome inhibitors, suggesting proteasome-associated degradation in skin cancer cells (Choudhury 2011). It also inhibits p38 MAPK and the proteasome activities, leading to inhibition of B cell lymphoma-extra large (Bcl-xL) phosphorylation and induction of prostate cancer cell death (Kazi et al. 2002). In patients with cancer of the head and neck or the pelvic region, topical treatment with green or black tea extracts suppressed cytokine release and inhibited the 26S proteasome function, which further resulted in NF-κB inhibition (Pajonk et al. 2006). EGCG also exhibited neuroprotective effects, inhibiting neuronal cell death by suppressing rapid PKC-mediated degradation of the Bad protein by the proteasome pathway (Kalfon et al. 2007).

Mutant p53 proteins are largely accumulated in cancer cells due to their increased stability, therefore targeting mutant form of p53 have shown to be an attractive approach for cancer therapy. In MDA-MB-435 cells, gambogic acid (GA)

(an active component of kokum) downregulates mutant p53 at the posttranscription level. The downregulation of mutant p53 by GA was mediated through the chaperones-assisted ubiquitin/proteasome degradation pathway in cancer cells (Wang et al. 2011). It has been also observed that at the posttranslational level, GA promoted the autoubiquitination of MDM2, followed by proteasome-mediated degradation. Additionally, GA increased p21(Waf1/CIP1) expression in p53-null cancer cells, which was associated with GA-mediated impairing of the interaction between MDM2 and p21(Waf1/CIP1). Furthermore, the apoptosis, cytotoxicity, and G(2)/M cell cycle arrest induced by GA was detected in both p53 wild-type and p53-null cancer cells (Rong et al. 2009). Another study showed that the combination of natural product GA and the proteasome inhibitor MG132 or MG262 resulted in a synergistic inhibitory effect on growth of malignant cells and tumors in allograft animal models (Huang et al. 2011). GA also inhibits the multidrug-resistant protein ATP-binding cassette transporter B1 (ABCB1). GA functions as a non-competitive inhibitor of ABCB1 by reducing its expression levels by promoting protein degradation through the post-translational proteasome pathway. Thus, GA can act as an anti-multidrug-resistance agent (Wang et al. 2013).

9.5 Role of Nutraceuticals in the Prevention and Treatment of Cancer

Because of their multi-targeting nature, cost-effectiveness, efficacy, safety, and immediate availability, nutraceuticals derived from dietary sources have attracted the attention of clinicians and researchers for cancer therapy (Gupta et al. 2011b, 2012). These dietary agents have been shown to modulate every facet of tumor development, including survival, proliferation, invasion, angiogenesis, and metastasis. In this section, we discuss some of the most promising nutraceuticals, including γ-tocotrienol, 6-gingerol, allicin, allyl isothiocyanate, apigenin, betulinic acid, caffeic acid, capsaicin, curcumin, diallyl disulfide, EGCG, emodin, evodiamine, fisetin, GA, genistein, indole-3-carbinol, myricetin, plumbagin, quercetin, resveratrol, sulforaphane, thymoquinone, ursolic acid, and xanthohumol in the context of five specific processes of tumorigenesis: survival, proliferation, invasion, angiogenesis, and metastasis.

One of the characteristic features of cancer cells is that they are able to grow in a rapid and uncontrolled manner and evade apoptosis. Cancer cells acquire this property through upregulation in cell survival proteins and downregulation in pro-apoptotic proteins (Ambrosini et al. 1997; Wang et al. 2003). Therefore, selective downregulation of cell survival proteins and upregulation of pro-apoptotic proteins in cancer cells represent promising therapeutic interventions for cancer therapy. Several nutraceuticals can affect tumor cell survival by inducing apoptosis through the modulation of numerous cell-signaling molecules. Depending upon the cancer types and inducers, nutraceuticals can modulate numerous targets. The most

common targets of nutraceuticals related with tumor survival are apoptotic protease activating factor-1 (Apaf-1), Bcl-2 homologous antagonist/killer (Bak), Bax, Bcl-2, Bcl-xL, Bcl-2–interacting mediator of cell death (Bim), Bcl-2-related gene expressed in fetal liver protein A1 (Bfl-1/A1), caspases, death receptors, FLIP, inhibitor of apoptosis protein (IAP), myeloid cell leukemia-1 (Mcl-1), NF-κB, p53 upregulated modulator of apoptosis (PUMA), signal transducers and activators of transcription protein-3 (STAT-3), and X-chromosome-linked IAP (XIAP) (Prasad et al. 2012a).

Curcumin, a component of golden spice, is a potent inducer of apoptosis in cancer cells. Curcumin induces apoptosis in cancer cells by upregulation of pro-apoptotic proteins (Bax, Bim, Bak, PUMA) and through downregulation of the cell survival proteins (Bcl-2, Bcl-xL) (Shankar and Srivastava 2007; Shankar et al. 2008). GA-induced apoptosis in MCF-7 cancer cells through upregulation of p53 and downregulation of Bcl-2 (Gu et al. 2009). The induction of apoptosis in human malignant melanoma A375 cells by GA was associated with an increase in Bax expression and a decrease in Bcl-2 expression (Xu et al. 2009). Resveratrol, a component of red wine-induced apoptosis in human multidrug-resistant SPC-A-1/CDDP cells through downregulation in survivin expression (Zhao et al. 2010). Some nutraceuticals have been shown to enhance the apoptosis induced by TRAIL in cancer cells. For instance, xanthohumol, a chalcone, enhanced TRAIL-induced apoptosis in prostate cancer cells (Szliszka et al. 2009).

Capsaicin was shown to sensitize malignant glioma cells to TRAIL-mediated apoptosis *via* death receptor 5 upregulation and survivin downregulation (Kim et al. 2010). Most nutraceuticals induce apoptosis by inhibiting NF-κB activation and expression of NF-κB regulated cell survival proteins. For instance, the induction of apoptosis in breast cancer cells was mediated through inactivation of Bcl-2 and the DNA binding activity of NF-κB (Ahmad et al. 2008). Fisetin was found to induce apoptosis in chemoresistant human pancreatic AsPC-1 cells through suppression of NF-κB activation (Murtaza et al. 2009). Sulforaphane inhibited the survival of orthotopically implanted PC-3 tumors through inhibition of NF-κB activation pathways (Shankar et al. 2008). Nutraceuticals have also been shown to inhibit the survival of tumor cells through the modulation of STAT-3 pathway. For instance, capsaicin has been reported to induce apoptosis in multiple myeloid cells through downregulation of STAT-3-regulated expression of Bcl-2, Bcl-xL, and survivin (Bhutani et al. 2007).

An ability to generate growth signals and insensitivity to antigrowth signals is another characteristic of cancer cells (Hanahan and Weinberg 2000). The most common way by which cancer cells acquire these features is through modulation of signaling molecules, including cdc25c, CDK, check point kinase (Chk), c-Myc, COX-2, p21-activated kinase 1 (PAK1), and retinoblastoma protein (Rb). The pro-inflammatory transcription factors NF-κB and STAT-3 are the important mediators of tumor proliferation. Nutraceuticals have been shown to suppress tumor growth by modulating one or more of these signaling molecules (Gupta et al. 2011a).

Most nutraceuticals prevent the transition of cancer cells from the G1 phase to the S phase. Some of these nutraceuticals act through p53 and some through Rb.

For instance, emodin showed anti-proliferative activity through a p53- and p21-dependent pathway and arrested liver cancer HepG2 cells in the G1 phase (Kuo et al. 2002). Fisetin was shown to arrest prostate cancer LNCaP cells at the G1 phase, which was associated with a decrease in cyclin-D1, -D2, and -E and their activating partners CDK-2, -4, and -6 and with the induction of p21 and p27 (Khan et al. 2008). The suppression in proliferation of epithelial ovarian cancer cells by sulforaphane was mediated through G1 cell cycle arrest, reduction in pRb, and in free E2F-1, and an increase in Rb (Bryant et al. 2010). Some nutraceuticals prevent tumor cell proliferation by preventing transitions from the G2 phase to the M phase. Evodiamine exhibited anti-proliferative activity by arresting human thyroid ARO cancer cells at the G2/M phase, which was associated with decreased expression of cdc2-p15 (Chen et al. 2010). GA suppressed proliferation of HepG2 and A549 cells by inducing p53/p21 activation and G2/M arrest (Rong et al. 2009). Betulinic acid evoked an increase in the G2/M phase population and a decrease in the S phase population in human gastric adenocarcinoma cells (Yang et al. 2010).

NF-κB has been shown to bind to the promoter of genes involved in cellular proliferation. A few nutraceuticals target one or more steps in NF-κB activation to regulate tumor cell proliferation. For instance, inhibition of ovarian cancer growth by curcumin was correlated with inhibition in NF-κB and a STAT-3 activation pathway (Lin et al. 2007). Curcumin also exhibited anti-proliferative activity in breast cancer cells in association with decreased expression of cyclin-D1 and CDK-4 (Liu et al. 2009). Over the past two decades, we have identified a number of nutraceuticals that suppress tumor proliferation through modulation of the NF-κB signaling pathway.

Tumor cell invasion is a process that involves cell growth, cell adhesion, cell migration, and proteolytic degradation of tissue barriers such as the extracellular matrix and basement membrane. Several proteolytic enzymes, including MMPs and the intercellular adhesion molecule, participate in the degradation of these barriers. A number of studies in lung, colon, breast, and pancreatic carcinomas have demonstrated overexpression of MMPs in malignant tissues compared to adjacent normal tissues. MMP-9 is upregulated in angiogenic dysplasia and invasive cancers and has been attributed to infiltrating inflammatory cells. Various nutraceuticals have been shown to inhibit the expression of MMP-9 in tumor cells, which leads to the inhibition of invasion and metastasis. These include curcumin (Anto et al. 2002; Shishodia et al. 2003; Kamat et al. 2007), resveratrol (Banerjee et al. 2002), disogenin (Shishodia and Aggarwal 2006), plumbagin (Sandur et al. 2006), indole-3-carbinol (Takada et al. 2005a), thymoquinone (Sethi et al. 2008), GA (Pandey et al. 2007), and betulinic acid (Takada and Aggarwal 2003). We have shown that curcumin inhibits the expression of MMP-9 in orthotopically implanted pancreatic tumors (Kunnumakkara et al. 2007) and ovarian tumors in nude mice (Lin et al. 2007).

Angiogenesis, driven by VEGF, is known to be a crucial process for tumor development. Since the role of angiogenesis in tumor development was first revealed (Folkman et al. 1971), a number of anti-angiogenic compounds have been developed, including bevacizumab (Avastin), sunitinib (SUTENT), sorafenib

(Nexavar), cediranib maleate (Recentin), and pazopanib (Gordon et al. 2010). We have identified several nutraceuticals that can suppress the expression of VEGF, including curcumin (Kunnumakkara et al. 2007, 2008), resveratrol (Aggarwal et al. 2004; Harikumar and Aggarwal 2008), ursolic acid (Prasad et al. 2012b), thymoquinone (Sethi et al. 2008; Yi et al. 2008), γ-tocotrienol (Ahn et al. 2007), and GA (Pandey et al. 2007). Our group also showed that curcumin has the ability to inhibit the expression of VEGF in pancreatic cancer patients (Dhillon et al. 2008).

Metastasis, a highly complex process, occurs in as many as 90 % of cancer-associated deaths and involves interactions between the cancer cells and the host. Numerous molecules have been linked with cancer metastasis including MMPs, VEGF, TNF, platelet-derived growth factor, transforming growth factor (TGF)-β, and twist transcription factor. Several studies have suggested that cancer cells express chemokine receptors that mediate metastasis to target organs expressing their cognate chemokines. One of the well-studied chemokines in tumor cell migration and metastasis is a stromal cell-derived factor 1α (SDF-1α, also known as CXC chemokine ligand 12 (CXCL12)) and its receptor, CXCR4. Different cancers preferentially metastasize to different organs, and production of SDF-1α by an organ is responsible for the migration of cancer cells to that organ. CXCR4 has been linked with tumor metastasis in a wide variety of cancers. Because CXCR4 binds to its ligand CXCL12, leading to tumor migration, agents that can interrupt the CXCR4-CXCL12 cell-signaling pathway have the potential to suppress tumor metastasis. We have identified several compounds that can suppress chemokine signaling and thus have potential for suppression of cancer metastasis. The most common nutraceuticals known to modulate tumor metastasis include curcumin (Lin et al. 2007; Kunnumakkara et al. 2009), demethoxycurcumin (Yodkeeree et al. 2010), allyl isothiocyanate (Yodkeeree et al. 2010), apigenin (Way et al. 2004), caffeic acid (Park et al. 2005), capsaicin (Shin et al. 2008), diallyl disulfide (Thejass and Kuttan 2007), evodiamine (Takada et al. 2005b), fisetin (Liao et al. 2009), genistein (Valachovicova et al. 2004), [6]-gingerol (Lee et al. 2008), indole-3-carbinol (Meng et al. 2000), quercetin (Vijayababu et al. 2006), resveratrol (Liu et al. 2010b), sulforaphane (Shankar et al. 2008), γ-tocotrienol (Liu et al. 2010a), and ursolic acid (Prasad et al. 2012b).

9.6 Conclusion

In the past several years, numerous studies have advanced our understanding of the mechanisms by which the nutraceutical acts as an anticancer agent. Nutraceuticals induce apoptosis and tumor regression in a broad spectrum of tumor cell lines, and in *in vivo* xenograft models. These nutraceuticals have been shown to have the ability to overcome drug resistance and to synergize with a number of conventional therapies through modulation of inflammatory transcription factors and other signaling molecules. Nutraceuticals have also been shown to inhibit the proteasome

pathway that might contribute to their anticancer activities. However, studies are required to demonstrate whether nutraceuticals can inhibit the proteasome pathway in cancer patients.

Acknowledgements We thank Luanne Jorewicz from the Department of Scientific Publications for carefully proofread the manuscript and provide valuable comments. Dr. Aggarwal is the Ransom Horne, Jr., Professor of Cancer Research. This work was supported by a grant from the Malaysian Palm Oil Board, Malaysia and a grant from Center for Targeted Therapy of MD Anderson Cancer Center.

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