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Review Article

Triphala: The Thai traditional herbal formulation for cancer treatment

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Abstract

Nowadays, Thai herbal plants are widely accepted in alternative medicine for treatment patients suffering deleterious diseases such as cancer. Having a variety of indications, several herbal formulas including Triphala have been routinely used as health tonic in Thai traditional and Ayurvedic medicines. The formulation of Triphala is a mixture of fruits of three plants: *Phyllanthus emblica* Linn., *Terminalia chebula* Retz. and *Terminalia bellerica* (Gaertn.) Roxb., all of which were reported to inhibit the growth and induce the death of cancer cells effectively. Therefore, anticancer activities inevitably turn out to be one of the essential properties of Triphala formula as well. It is likely that a number of active compounds in the formula, especially tannins, are the key agents that induce the apoptotic cell death via free radical production in cancer cells. On the other hand, all three fruits of these plants also contain high levels of antioxidants, capable of protecting normal cells from any free radical-mediated injuries effectively. Thus, the paradoxical role of Triphala is cell-type specific and becomes an advantage for usage of this formulation. Furthermore, Triphala has high potentials for inhibition and prevention of mutagenesis and metastasis of cancer cells. Finally, studies in the mechanism of action of Triphala and the product development as well as safety evaluation of the standard herbal extract are definitely required for future pharmacological applications of Triphala as anticancer agents for cancer therapy.

Keywords: Triphala, *Phyllanthus emblica* Linn., *Terminalia chebula* Retz., *Terminalia bellerica* (Gaertn.) Roxb., anticancer, antioxidant

1. Introduction

Cancer is one of the most deadly illnesses and also becomes one of the top leading causes of death world-wide. The use of medicinal plants or bioactive plant derived compounds has now aroused a lot of interest and research in the prevention and treatment of cancer. Yet, a lack of scientific evidences has slowed down the development of herbal medicine for pharmacological applications. A traditional formulation of herbal medicine usually contains a variety of constituents such as polyphenol, alkaloids, flavonoids, triterpenoids, and other secondary metabolites that have anticancer/ antimutagenic properties (Newmark, 1996; Surh, 1999; Singh and Agarwal, 2006) This review aims to give an overview on the recent scientific information of Triphala, a Thai traditional herbal formulation with potential for the prevention and treatment of cancer.

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Table 1. Components of Triphala

Elements	Ratios		
	Phyllanthus emblica Linn.	*Terminalia chebula* Retz.	*Terminalia bellerica* (Gaertn.) Roxb.
Pitta or bile (fire + water)	4	8	12
Vata or wind (air + space)	8	12	4
Kapha or mucous (water + earth)	12	4	8
Malas or waste product (feces)	8	8	8

Triphala has commonly been used in an Ayurvedic and traditional Thai medicines. It consists of the dried fruits of three plants, *Phyllanthus emblica* Linn. (or *Emblica officinalis* Gaertn., Indian gooseberry, Amalaki, Ma-kham-pom), *Terminalia chebula* Retz. (Chebulic myrobalan, Haritaki, Sa-mor-Thai) and *Terminalia bellerica* (Gaertn.) Roxb. (Belleric myrobalan, Vibhitaka, Sa-mor-Phe-phek). As listed in Table 1, different proportions of Triphala are based on body types, or elements of the human body. Triphala has been described as an important health tonic for detoxification, rejuvenation, and balance, especially in the summer season (Gaind *et al*., 1963; Rege *et al*., 1999; Jagetia *et al*., 2002). It is a therapeutic agent for treatment of a variety of conditions such as headache, dyspepsia, constipation, liver conditions, fatigue, infections and assimilation, and is also reported to possess many biological activities including antidiabetic (Sabu and Kuttan, 2002), antimutagenic (Kaur *et al*., 2002), antimicrobial (Mehta *et al*., 1993), radioprotective (Jagetia *et al*., 2002), hypocholesterolaemic (Thakur *et al*., 1988), antiviral (El-Mekkawy and Merelhy, 1995), immunomodulatory (Srikumar *et al*., 2005), and anticancer (Kaur *et al*., 2005), etc.

Figure 1. The dried fruits of *Phyllanthus emblica* Linn., *Terminalia chebula* Retz. and *Terminalia bellerica* (Gaertn.) Roxb.

2. *Phyllanthus emblica* Linn.

Phyllanthus emblica Linn. (syn. *Embica officinalis* Gaertn.) belongs to Family Euphorbiaceae and is commonly known as emblic myrobalan, Indian gooseberry, amla, amalaka, and ma-kham-pom in Thai. The plant is widely found in all tropical deciduous forests of South and Southeast Asia. The fruit is spherical (15-33 mm), greenish-yellow and drupaceous with six vertical furrows (Figure 1). The major constituents of *P. emblica* include a number of tannins, flavonoids, and other phenolic compounds. The fruits contain low molecular weight tannoids, mainly emblicanins A and B, punigluconin and pedunculagin, and gallic acid (Zhang *et al*., 2001a). Furthermore, organic acid gallates and other hydrolysable tannins including 1-*O*-galloyl-b-D-glucose, corilagin, chebulagic acid, elaeocarpusin, and puntranijivan A have been isolated from the fruit juice of *P. emblica* (Zhang *et al*., 2001b). It is one of the most commonly used in many local traditional medicine systems including Ayurvedic and Chinese medicine as well as Thai herbal medicine. The fruits of this plant have been used for treatment of various ailments, such as anemia, liver disease, dyspepsia, hemorrhage, jaundice and diarrhea (Chawla *et al*., 1982). The extracts of *P. emblica* have been shown to possess several biological activities, e.g. analgesic, antipyretic (Perianayagam *et al*., 2004), antimicrobial, anti-inflammatory (Asmawi *et al*., 1993), antioxidant (Bhattacharya *et al*., 1999), antiviral, antimutagenic (Grover and Kaur, 1989), antidiabetic (Sabu and Kuttan, 2002), and anticancer (Jose *et al*., 2001; Rajeshkumar *et al*., 2003). In addition, it has been found to have a protective effect upon radiation-induced chromosomal damage and also hypocholesterolemic (Kim *et al*., 2005), hypolipidemic (Mathur *et al*., 1996), cardioprotective (Tariq *et al*., 1977) and anti-atherosclerotic in both humans and experimental animals (Thakur and Mandal, 1984). The fruit extracts of *P. emblica* also possess radioprotective effect

against gamma irradiation (Hari Kumar *et al*., 2004) and *in vivo* heptatoprotective activities against CCl_4 (Lee *et al*., 2006a), paracetamol (Gulati *et al*., 1995), ethanol (Pramyo-thin *et al*., 2006) and antituberculosis drugs (Tasduq *et al*., 2005). Furthermore, several *in vivo* studies have shown inhibitory effect of *P. emblica* on clastogenecity of benzopyrene and cyclophosphamide (Sharma *et al*., 2000), as well as cytoprotective activities against heavy metals (Khandelwal *et al*., 2002), oxidative stress in ischemic-reperfusion injury (Rajak *et al*., 2004) and DMBA-induced genotoxicity (Banu *et al*., 2004).

3. *Terminalia bellerica* (Gaertn.) Roxb and *Terminalia chebula* Retz

Terminalia bellerica (Gaertn.) Roxb. (syn.: *Myrobalanus bellerica* Gaertn.) and *Terminalia chebula* Retz. (syn.: *Myrobalanus chebula*, Gaertner) belong to the Family Combretaceae. Both of these plants are widely cultivated in South and Southeast Asia including Thailand. *T. bellerica* is well-known as belleric myrobalan, Bihara or Bahera in India, and samor-phiphek in Thailand. The fruit is a drupe, globose or ovoid, 1.3 to 1.9 cms in diameter, covered with wooly hairs with a hard thick walled light yellow putamen, 1-seeded, surrounded by a green tissue (Figure 1). The fruit contains tannins as a major component, both condensed and hydrolysable such as gallic acid, ethyl gallate, and ellagic. Other constituents identified in the fruit include β-sitosterol, belleric acid, chebulagic acid, glucose, glycosides and various carbohydrates (Mahato *et al*., 1992; Nandy *et al*., 1989). *T. bellerica* has been widely used as a laxative as well as an astringent, and also as traditional medicine for several ailments such as fever, cough, diarrhea, oral thrush, inflammation, dyspepsia, skin and liver diseases. Other biological activities of the fruit extract have been reported to possess antimicrobial (Elizabeth, 2005; Nandy *et al*., 1997), anti-HIV, antimalarial, antifungal (Valsaraj *et al*., 1997), antidiuretic (Kar *et al*., 2003) and antimutagenic effects (Padam *et al*., 1996).

T. chebula is commonly known as black myrobalans in English, harada in Hindi, and samorthai in Thai. The ripe fruit is a hard glabrous drupe, 3-5 cm. long, ellipsoid to oval in shape with yellowish orange brown, and containing a single seed, usually 2 cm. long and 1 cm. in diameter (Figure 1). When dry the fruit becomes five-ridged. *T. chebula* fruit contains high phenolic content, especially hydrolysable tannins. The structures of the 14 hydrolysable tannins in the fruit of *T. chebula* are gallic acid, chebulic acid, punicalagin, casuarinin, chebulanin, corilagin, neochebulinic acid, terchebulin, ellagic acid, chebulagic acid, chebulinic acid, 1,6-di-O-galloyl-D-glucose, 3,4,6-tri-O-galloyl-D-glucose, and 1,2,3,4,6-penta-O-galloyl-D-glucose (Lee *et al*., 1995; Juang *et al*., 2004). *T. chebula* has been traditionally used in folk medicines as a laxative, diuretic, cardiotonic, digestive, antiseptic, and carminative (Barthakur and Arnold, 1991). In addition, *T. chebula* has been reported to exhibit a variety of biological activities including antimutagenic (Grover and Bala, 1992; Kaur *et al*., 1998), antimicrobial (Sato *et al*., 1997), antiviral (Kim *et al*., 2001; Kurokawa *et al*., 1995), antianaphylaxis (Shin *et al*., 2001), anticancer (Saleem *et al*., 2002), antioxidant and free radical scavenging activities (Cheng *et al*., 2003). It also has a potent protective effect against oxidative stress-induced hepatotoxicity (Na *et al*., 2004).

4. The anticancer activity of Triphala

Triphala becomes one of the highly potential herbal medicines in cancer treatment and prevention because all three compositions of Triphala have been found to possess notable anticancer properties (Sandhya *et al*., 2006a). Although very little is known about the mechanism by which these plants act against cancer cells, the anticancer effect of Triphala has been recently investigated and supported by several lines of evidence from studies of each plant component.

The anticancer activity of *P. emblica* has been demonstrated by several reports. Extracts of *P. emblica* fruit inhibited the proliferation of a variety of tumor cell lines *in vitro* (Zhang *et al*., 2004). A number of compounds isolated from different parts of this plant were determined as active components, especially compounds with a galloyl or pyrogallol group. The aqueous extract of the fruit was cytotoxic to L 929 cells and able to reduce ascites tumor in mice induced by DLA cells. It also increased life span of tumor-bearing mice and reduced tumor volume effectively (Jose *et al*., 2001). The anticarcinogenic activity of the extracts has been reported. The extracts of *P. emblica* significantly inhibited hepatocarcinogenesis induced by N-nitrosodiethylamine in animals (Jeena *et al*., 1999). The fruits of *P. emblica* alleviated the immunosuppressive effects of chromium on lymphocyte proliferation and restored the production of IL-2 and interferon-γ (Sai Ram *et al*., 2002). In addition, the aqueous fruit extract of *P. emblica* possesses a chemopreventive effect on DMBA-induced skin tumorigenesis in mice (Sancheti *et al*., 2005).

The underlying mechanism by which *P. emblica* inhibits cancer cells is still not clear. Several possible mechanisms have been proposed involving an interference with the cell cycle (Jose *et al*., 2001). The extract showed a cell-cycle specific inhibition by inhibiting cdc25 phosphatase and cdc 2 kinase. The anticancer activity may be mediated through enhanced natural killer cell activity and antibody-dependent cellular cytotoxicity. Since free radical and lipid peroxidation are also well known to involve tumor initiation and promotion (Sanchez-Perez *et al*., 2005), combined activity of antioxidants present in *P. emblica* also likely is responsible for the anticarcinogenic as well as chemopreventive activities.

T. chebula, another constituent of Triphala, has also been found to possess the cytotoxic effects against human cancer cell lines (Lee *et al*., 1995). The metanolic extract of *T. chebula* containing gallic acid, 1,2,3,4,6-penta-*O*-galloyl-

D-glucopyranose, chebulagic acid, and chebulinic acid inhibited growth of human cancer cell lines including A-549, SK-OV-3, SK-MEL-2, XF-389, and HCT-15. In addition, Saleem *et al*. (2002) has studied the cytotoxic effects of *T. chebula* fruit extract in several human cancer cell lines including breast cancer (MCF7), osteosarcoma (HOS-1) and prostrate cancer (PC-3). The results showed the 70% methanol extracts inhibited cell proliferation, and induced cell death in a dose dependent manner. At lower concentration (8.0-40.0 μg/ml), a treatment of the metanolic extract of *T. chebula* for 72 h induced apoptotic cell death, whereas at higher concentration (>40 μg/ml) necrotic cell death was observed. The cytotoxic effect of several phenolic compounds and tannic acid in *T. chebula* was also determined by ATP level. The most potent cytotoxic compounds were chibulinic acid (IC_{50} = 53.2 μM) and tannic acid (IC_{50} = 59.0 μg/ml). The ellagic acid (IC_{50} = 78.5 μM) and 2,4-chebulyl-β-D-glucopyranose (IC_{50} = 120 μM) showed less cytotoxic activity as compared to chebulinic acid. These results concur with other studies in which the phenolic compounds, especially hydrolysable tannins exhibit cytotoxic activity and induce apoptotic cell death in various cancer cell lines (Yang *et al*., 2000; Sakagami *et al*., 2000). Thus, these phenolic compounds and their derivatives are likely responsible for the biological activities of *T. chebula*.

The anticancer effects of Triphala at equal proportions of each plant extracts have been investigated by a few studies. The aqueous extract of Triphala was toxic both on human breast cancer cell line (MCF7) and a transplantable mouse thymic lymphoma (barcl-95) (Sandhya *et al*., 2006a). Triphala at the same concentration induced a 3-5 times higher toxicity in the cancer cells as compared to the normal cells. The morphology of tumor cells showed distinct alterations similar to apoptotic cells. The apoptotic cell death induced by Triphala was further confirmed by annexin-V staining for phosphatidylserine (PS) externalization. In addition, Triphala induced the pattern of DNA fragmentation, which is a characteristic of apoptosis in tumor cells. Oral administration of Triphala in mice 7 days after tumor transplantation caused significant reduction in tumor volume. The mechanism of *in vitro* cytotoxicity and tumor growth reduction *in vivo* induced by Triphala seems to involve apoptosis induction. In addition, the components of Triphala may exert synergistic cytotoxic action on tumor reduction.

Gallic acid is one of the major components of Triphala and capable of inhibiting cancer cell proliferation suggesting the key factor responsible for antimutagenic and cytotoxic effects of Triphala (Kaur *et al*., 2005). Ishihara and Sakagami (2003) have reported cytotoxic activity of gallic acid against human leukemia (HK-63) cell line. Saleem *et al*. (2002) also reported that gallic acid exhibits cytotoxic effect in HOS-1 cell line. Similarly, gallic acid showed higher cytotoxicity against HSC-2 (Furuya *et al*., 2001) by producing DNA fragmentation as compared to normal HGF cells. Similarly, several gallic acid derivatives including ethylgallate 2,3,4-trihydroxybenzoic acid and ellagic acid have been shown to induce apoptotic cell death in various cancer cell lines (Han *et al.,* 2006).

The cytotoxic mechanism of Triphala has been further studied using two human breast cancer cell lines that differ in their p53 status (Sandhya and Mishra, 2006). Treatment of MCF7 cells with Triphala at low concentration (5-10 μg/ml) caused 50% loss of cell viability and apoptotic cell death. The cancer cell line (MCF7) with wild type p53 was more sensitive to Triphala than the p53 negative cell line. Pifithrin-alpha, a specific inhibitor of p53, was able to block Triphala induced cytotoxicity in MCF-7 cells, indicating p53 dependent toxicity. On the other hand, the inhibitor failed to block the toxicity effect on the cells with p53 mutant, suggesting an mechanism by which Triphala induced cytotoxicity via p53 dependent pathway. The p53 status of cancer cells seemed to be an important factor in predicting the response of cancer cells to prooxidant drugs.

Polyphenols such as tannins and gallic acid, a component unit of hydrolysable tannins, are well known inducers of apoptosis in tumor cells (Inoue *et al*., 2000). Their cytotoxicity of tumor cells involved a reactive oxygen species (ROS) mediated mechanism. P53 is a redox sensitive gene whose transcription can be induced by several prooxidants (Schwartz *et al*., 1993). Therefore, the expression of redox-responsive genes such as the p53 gene is possibly activated to regulate intracellular ROS production. Subsequently, excessive level of oxidative stress triggers the cell to program cell death (Engel and Evens, 2006; Renschler, 2004). Thus, prooxidant agents are capable of inducing apoptosis in the p53 wild type cancer cells. In addition, exogenous addition of antioxidants, glutathione and N-acetyl-cysteine (NAC) reversed the anti-proliferative effects of Triphala in both cell lines. These suggest a role of Triphala in the generation of ROS causing the induction of apoptosis.

5. The paradoxical effects of Triphala: prooxidant vs antioxidant

The action of Triphala as a prooxidant has been verified in cancer cells. Using DCH-FDA fluorescent probe, a significant increase in intracellular ROS level was detected in tumor cells, but not normal cells treated with Triphala (Sandhya *et al*., 2006a). Plant polyphenolic compounds are capable of inducing cytotoxicity via generation of ROS (Sakagami *et al*., 2000; Nogaki *et al*., 1998). The induction of apoptotic death in tumor cells by Triphala seems related to the generation of cytoplasmic ROS subsequently leading to cellular oxidative damage (Figure 2). Gallic acid, a major component in Triphala, could be responsible for the cytotoxic effects as it has been shown to kill tumor cells through hydrogen peroxide generation (Perego *et al*., 2000; Sakagami *et al*., 2001).

The roles of free radical including reactive oxygen and nitrogen species, however, are often linked with the pathological state of numerous diseases (Vendemiale *et al*., 1999). These agents effectively oxidize and subsequently damage

cellular macromolecules. Many of the free radicals are highly genotoxic and cause formation of other carcinogenic compounds that lead to mutagenesis and initiation towards the process of carcinogenesis (Valko *et al*., 2004). Saleem *et al*. (2001) has reported that among 37 medicinal plants extracts, *T. chebula* fruit extract has higher phenolic content and stronger *in vitro* lipid peroxidation inhibition capacity. A number of phenolic compounds have been reported for their antitumor and anticarcinogenic activities (Gali *et al*., 1992; Gali-Muhtasib *et al.,* 1999). They may be blocking agents of metabolite activation of promutagen and then forming adducts with the mutagens and scavenging of free radicals (Figure 2).

An antimutagenic potential of water, chloroform and acetone extracts of Triphala has been evaluated by an Ames Test using TA98 and TA100 strains of *Salmonella typhimurium* against the mutagens, 4-nitro-o-phenylenediamine (NPD) and sodium azide, and the promutagen, 2-aminofluorene (2AF) in the presence of phenobarbitone-induced rat hepatic S9. Only the chloroform and acetone extracts showed strong inhibition of mutagenicity induced by both direct and S9-dependent mutagens (Kaur *et al*., 2002).

In vitro antioxidant and free radical scavenging activities of Triphala and its constituents have been evaluated (Vani *et al*., 1997). Triphala and its individual components are capable of scavenging free radicals DPPH, superoxide, and nitric oxide (Naik *et al*., 2005; Jagetia *et al*., 2004). *T. chebula* possesses maximum free radical scavenging ability which possibly relates to the high content of polyphenol, gallic acids present in the extract. Furthermore, *T. chebula* is considered to possess the best antioxidant activity as compared with other extracts of herbal medicine including *Momordica charantia* Linn, *Glycyrrhiza glabra*, and *Acacia catechu* (Naik *et al.,* 2003). Six extracts (MeOH, $CHCl_3$, EtOAc, n-butanol, organic aqueous, and water) and four compounds (casuarinin, chebulinic acid, chebulanin, and 1,6-di-*O*-galloyl-β-D-glucose) of *T. chebula* possess anti-lipid peroxidation, anti-superoxide formation and free radical scavenging activities (Cheng *et al*., 2003). Among the tested extracts and pure compounds, chebulanin exhibited the most potent anti-lipid peroxidation and anti-superoxide formation activities while chebulinic acid had the strongest free radical scavenging activity. The antioxidant activity of *T. chebula* seems to be derived from various specific pathways.

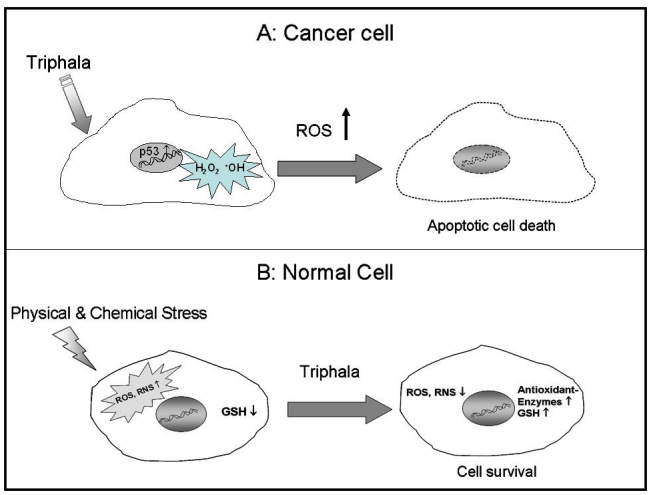

Figure 2. Paradoxical roles of triphala as prooxidant in cancer cell (A) and antioxidant in normal cell (B) (ROS: Reactive oxygen species, RNS: Reactive nitrogen species, GSH: glutathione)

The antioxidant effects of *T. chebula* fruit extract were further extensively characterized and confirmed by other several studies. The ethanol extract of *T. chebula* significantly inhibited oxidative stress induced by tertiary butyl hydroperoxide and ultraviolet-B irradiation (Lee *et al*., 2005; Na *et al*., 2004). In addition, the *T. chebula* extract inhibited the age-dependent shortening of the telomeric DNA length *in vitro* suggesting the anti-aging effect of *T. chebula*. These studies have provided significance evidence of the antioxidant activities which possibly relate to other biological activities of *T. chebula*. Furthermore, both aqueous and ethanol extracts of the fruits of *T. chebula* exhibited hepatoprotective activity against oxidative stress in isolated rat hepatocytes (Lee *et al*., 2006b). Chebulic acid isolated from the *T. chebula* extract was identified as the hepatoprotective compound. The aqueous extract significantly restored the level of reduced glutathione (GSH) in rat liver, and treatment of hepatocytes with chebulic acid significantly attenuated the reduced GSH level. Thus, the compound exhibits both a free radical-scavenging and ferric-reducing antioxidant activities

The extracts of *P. emblica* have been shown to scavenge hydroxyl and superoxide radicals (Naik *et al*., 2005) and stimulate several antioxidant enzyme systems including catalase, superoxide dismutase, and glutathione peroxidase (Bhattacharya *et al*., 2000). The extract of *P. emlbica* has the ability to inhibit not only lipid peroxidation, but also radiation-induced damage to the superoxide dismutase in rat liver mitochondria (Khopde *et al*., 2001). Recently, geraniin isolated from *P. emblica* has been shown to be a compound with the highest nitric oxide scavenging activity (Kumaran and Karunakaran, 2006). Other nitric oxide scavenging components of *P. emblica* have also been identified as gallic acid, methyl gallate, corilagin, and furosin. Several antioxidant ingredients have been reported in this plant such as tannins, trugalloyl glucose, flavanoids, ellagic acid, phyllaemblic acid, gallic acid, and ascorbic acid, etc (Bhattacharya *et al*., 1999; Zhang *et al*., 2001c).

The fruits of *P. emblica* have long been believed to contain a large amount of vitamin C, and its antioxidant activities are thought to be primarily due to this factor (Jain and Khurdiya, 2004). Scartezzini *et al*. (2006) have shown that the fruits of *P. emblica* do indeed contain vitamin C (0.40% w/w), which accounts for 45-70% of the antioxidant activity. In contrast, Ghosal *et al*. (1996) and Bhattacharya *et al*. (1999) reported that the fruit of this plant does not contain vitamin C, but contains emblicanin A, emblicanin B, puningluconin, and pedunclagin which are responsible for

the antioxidant activity of the fruit. The two emblicanins exhibited the highest antioxidant effect, and could increase the efficacy of vitamin C in reducing dehydroascorbic acid to ascorbic acid. Therefore, it is possible that the recycling of ascorbic acid by these tannins could thereby increase the antioxidant activity of *P. emblica*.

Exposure to gamma-irradiation causes generation of hydroxyl radicals and the subsequent free radical induced strand breaks in DNA and lipid peroxidation. The aqueous extract of Triphala and its constituents effectively inhibits radiation-induced damage in both DNA and liver microsomal lipids suggesting the antioxidant activity under gamma-irradiation conditions (Naik *et al*., 2005). All three constituents of Triphala independently possess antioxidant activity in which *P. emblica* and *T. bellerica* show the greatest and lowest effectiveness, respectively. Chemopreventive effect of Triphala has recently been proved using benzo(a) pyrene induced forestomach tumorigenesis in mice. In long-term studies, tumor incidences and tumor burden were lowered to 65% and 50%, respectively, by Triphala mixed diet. The antioxidant status of animals was also increased significantly by Triphala (Deep *et al*., 2005).

Several factors such as stress condition and radiation cause an imbalance in the oxidant/antioxidant system. A stressful condition stimulates secretion of glucocorticoids, which is measured by plasma corticosterone level (Bauer *et al*., 2001). Stress is one of the important factors associated with progression of a number of chronic diseases including cancer. The effect of stress not only leads to the alteration in the antioxidant status, but also impairs immune response (Reiche *et al*., 2004). The excessive production and/or inadequate removal of free radicals results in oxidative stress that contributes to cellular damages. Thus, the role of antioxidants becomes increasingly important to protect the oxidation. The antioxidant effect of *T. chebula* has been further considered as a radioprotector, since ionizing radiation can lead to the damage of cellular organelles by producing excessive ROS (Gandhi and Nair, 2005; Naik *et al*., 2004). Administration of the aqueous extract of Triphala prior to irradiation exposure significantly reduced the peroxidation of membrane lipids as well as radiation-induced damage to DNA. Due to its antioxidant properties, administration of Triphala decreases lipid peroxidation and corticosterone levels in noise-stress induced rats (Srikumar *et al.*, 2006). In addition, Triphala possesses immunomodulatory activity as it stimulates the neutrophil functions (Srikumar *et al*., 2005).

Radiation is one of the most common practices for cancer treatment. Yet, cancer radiotherapy often causes serious side effects as the result of normal cell damage. Ionizing radiation can induce oxidative damage in the cellular macromolecules. The free radical scavenging activity of Triphala is likely an important underlying mechanism of its radioprotective ability. Triphala significantly inhibited radiation induced DNA damage as indicated by single cell gel electrophoresis (Sandhya *et al*., 2006b). A study in irradiated mice showed that oral feeding of Triphala for 7 days before and after irradiation reduced mortality by 60% (Srikumar *et al*., 2006). Triphala scavenges not only hydroxyl radicals, but also other dangerous free radicals such as superoxide anion and nitric oxide in a dose-dependent manner. In addition, Triphala reduces the activity of the free radical producing enzyme, xanthine oxidase, but not that of the antioxidant enzyme, superoxide dismutase. Consequently, the protection of mice by Triphala against radiation is also likely mediated through inhibition of oxidative damage by modulation of cellular enzymes.

6. Triphala as an antimetastatic agent

According to its strong inhibitory activity on matrix metalloproteinases, Triphala potentially could be developed as an inhibitor against tumor metastasis (Abraham *et al*., 2005). Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases which are capable of degrading extracellular martrix. These proteins play a pivotal role in a variety of physiological and pathological processes, including embryonic development, wound repair and tissue remodeling, inflammation, and cancer (Malemud, 2006). MMPs, especially MMP-2 and MMP-9, are often involved in tumor invasion and metastasis, as they specifically degrade type IV collagen, which is a major component of basement membrane. Several studies have reported the association of elevated MMP-2/9 expression with increased invasive potential of many tumor cells. A number of plant derived compounds including polyphenols have been shown to inhibit *in vitro* tumor invasion (Maeda-Yamamoto *et al*., 1999; Ho *et al*., 2002). Epigallocatechin-3-O-gallate (EGCG) inhibits the metallo and serine protease activities as well as tumor invasiveness (Benelli *et al*., 2002). In addition, hydrolysable tannins, such as 1,2,3-tri-O-galloyl-3,6-hexahydroxydiphenoyl-β-D-glucose (punicafolin) suppresses the invasion of HT1080 fibrosarcoma cells through the direct inhibition of MMP-2/-9 activity (Tanimura *et al.*, 2005). Although Triphala has the inhibitory activity against these MMPs, the inhibition on tumor cell-invasiveness of Triphala has not yet been clearly demonstrated, and it needs to be further elucidated.

7. Toxicity

A number of toxicity studies have been reported on both the extract of Triphala and on individual extract of *T. chebula*, *T. bellerica*, and *P. emblica*. One toxicity study of Triphala showed it was non-toxic up to a dose of 240 mg/kg at which no drug-induced mortality was observed (Jagetia *et al*., 2002). Another study on subacute toxicity in Wistar rats examined three different formulas of Triphala by a single oral administration daily for ten days at the doses up to 23.04 g/kg body weight/day (Chavalittumrong *et al*., 1996). The results showed that the Samha (or Kapha) extract showed no signs of the toxicities. In contrast, the female was more susceptible to toxic effects of Triphala extracts than the male. The female rats treated with the high dose of Pitta extract

had an incidence of fatty liver change and nephrocalcinosis, while the high dose of Wata extract caused both nephrocalcinosis and hydrocalyx in all groups of female rats.

The extracts of *T. chebula*, *T. bellerica*, and *P. emblica* have been considered as fairly safe. All extracts of these plants was not cytotoxic as determined by fresh sheep erythrocyte assay (Ahmad *et al*., 1998). The alcoholic fruit extract of *T. chebula* up to a dosage of 500 mg/kg body weight/day for 30 days did not cause signs of toxicity and mortality (Kumar *et al*., 2006). An acute toxicity study of *P. emblica* fruit extract showed a single-dose acute oral LD_{50} of > 5,000 mg/kg body weight in both male and female rats (Chaudhuri, 2002). In addition, the LD_{50} of the alcoholic extract of *T. bellerica* fruit was about 4.25 g/kg body weight (Siddiqui, 1963), while the aqueous extract was found to be non-toxic up to oral doses of 3.2 g/kg body weight in mice (Anand *et al.*, 1994).

8. Conclusion and future perspective

Triphala, a traditional Ayurvedic formulation, consists of the dried fruits of three plants, *Phyllanthus emblica* Linn., *Terminalia chebula* Retz. and *Terminalia bellerica* (Gaertn.) Roxb. Frequently used in many folk medicines, the herbal formulation possesses several pharmacological activities including anticancer. The cytotoxic effects of Triphala against many cancer cells likely involve ROS-induced apoptosis, suggesting the possible role of the extract as a prooxidant despite the high content of antioxidants. Based on several studies of the individual plants, several components such as gallic acid have been identified as active agents, yet the underlying mechanism is not fully elucidated. In contrast, due to its potent antioxidant properties, Triphala is capable of protecting normal cells against ROS-induced damages under several conditions such as radiation, stress, chemical, etc. Therefore, these results evidently show the promise of Triphala as a potential chemopreventive and/or anticancer drug. However, more than a few studies such as the cytotoxic effects of Triphala at different formulations; pitta, vata, and kapha on both *in vitro* and *in vivo*, etc. need to be done to gain more insights into the physiologically relevant mechanism(s) prior to any clinical applications.

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