

Full Length Research Paper

A systematic review of the antioxidant, anti-diabetic, and anti-obesity effects and safety of triphala herbal formulation

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Triphala (TPL) is one of the oldest used polyherbal preparations. It is comprised of *Terminalia chebula*, *Terminalia bellerica* and *Emblca officinalis*. A variety of uses, such as anti-obesity, of TPL have been described in Ayurvedic and Al-Qanoon Felteb literature. This study focuses on the efficacy and safety of triphala in medicines, with any outcome in humans and animals; and described some of the mechanisms responsible for the many effects of this traditional medicine and main phytochemical analysis. The databases searched include Google Scholar, PubMed, Web of Science, the search terms were "TPL" and "trifala" without narrowing or limiting search elements. The benefits of TPL *in vivo* and *in vitro* include: antioxidant, anti-hypercholesterolemic, anti-diabetic, anti-obesity, chemo-preventive potential and anti-mutagenic activity, anti-inflammatory, antimicrobial, radioprotective effect, immunomodulatory, improving wound healing, enteroprotective efficacies, anti gastric ulcers and nitric oxide scavenging activity. This herbal combination can have profound healing benefits in multi-organ systems. And, it exhibits a number of health benefits like antioxidant activity, lowers cholesterol. It is rich in Mg, K, Ca, Fe, Se and Zn, which enhance their bioavailability. TPL may be potent therapeutic agents for scavenging of NO and thereby help to explain, rejuvenating, adaptogenic, cardioprotective and neuroprotective activities of these traditional, and clinically used non toxic drugs.

Key words: Triphala, *Emblca officinalis*, *Terminalia chebula*, *Terminalia bellerica*, traditional medicine, anti-diabetic, antioxidant, anti-obesity, anti-mutagenic activity.

INTRODUCTION

Recently, complementary therapies are being used increasingly worldwide. When conventional medicine fails to treat chronic diseases efficaciously and without adverse events, many people seek unconventional

therapies including herbal medicine (Hasani-Ranjbar et al., 2009).

Triphala (TPL) is one of the oldest and most commonly used polyherbal preparations in the Indian system of

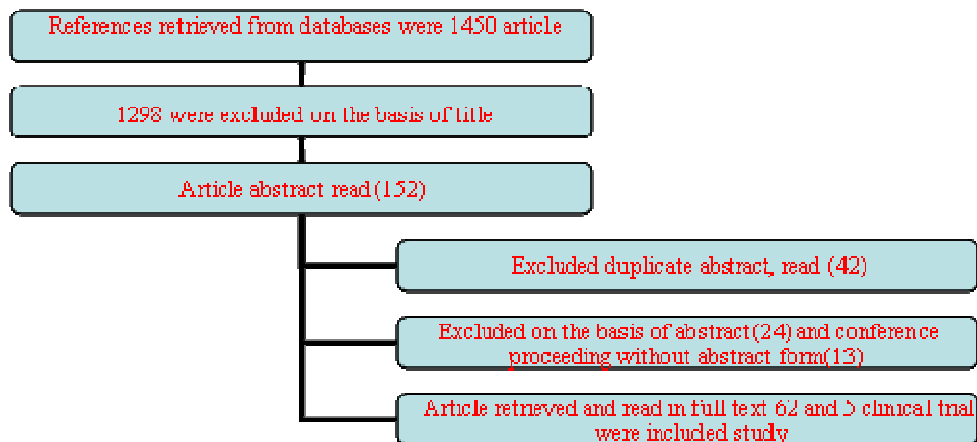


Figure 1. Flow of the study.

tri = three and phala = fruits), include the Arabicized “Atrifal” and the Chinese term “San-Teng” (Mahdihassan, 1978). This preparation is composed of three equal proportion (Sabu et al., 2002; Ibn-e-sina, 2005) of herbal fruits: *Terminalia chebula*, *Phyllanthus emblica*, and *Terminalia belerica* (Baliga., 2010; Ibn-e-sina., 2005).

A variety of therapeutic effects have been described in Ayurvedic for TPL including cardiovascular disorders, liver dysfunction, and for inflammation (Garg et al., 2005). TPL has been considered as an anti-obesity preparation in Al-Qanun Fit-Tib (Ibn-e-sina, 2005). Since there is no evidence based approach to show the beneficial effects of these formulation *in vitro* and *in vivo* trials, here we present the results of our systematic review on TPL to show the efficacy and safety of this medicinal plant in humans and animals.

METHODOLOGY

The databases searched include Google Scholar, PubMed, Web of Science, Cochrane library, SID, uptodate, irandoc and IranMedex up to July 8, 2011. The search terms were “TPL” and “trifala” without narrowing or limiting search elements. All human and animal studies that included the evidences of the effects of TPL with any outcome were selected for review. Clinical trials (any phase) were identified for data abstraction and observational studies. Only publications without available abstracts and letters to the editor were excluded from review. Unpublished data was also excluded from study. Duplication was avoided by excluding review of multiple copies of the same article in several databases.

RESULTS

Summary of references retrieved from databases included in the study are shown in Figure 1. This review for the first time summarizes these results, with emphasis on published observations. The efficacy and safety of TPL is summarized in Table 1.

Antioxidant

Many studies (Luo et al., 2011; Naik et al., 2004, 2005a, b; Shivaprasad et al., 2008; Singh et al., 2010; Palav et al., 2006; Perera et al., 2008; Pfundstein et al., 2010; Vani et al., 1997) have assessed the antioxidant activity of TPL. The antioxidant activities were determined by 1,1-diphenyl-2-picryl-hydrazyl (DPPH) method and inhibition of lipid peroxide formation induced by Fe^{2+} -ascorbate system. They were found to strongly correlate with total polyphenol contents (Palav et al., 2006). Mallotusin and mucic acid 1, 4-lactone 3-O-gallate were reported to have antioxidant activity (Luo et al., 2011). TPL has been found to be an excellent scavenger of hydroxyl radicals and nitric oxide radicals and is capable of increasing the capacity to tolerate non-specific stress in experimental animals (Shivaprasad et al., 2008). TPL was also effective in preventing superoxide-induced haemolysis of red blood cells (Vani et al., 1997).

Anti hypercholesterolemic

Hypercholesteremia is one of the risk factors for coronary artery diseases (Saravanan et al., 2007). Several studies assessed the efficacy of herbal formulation TPL on total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), and free fatty acid, experimentally and the results showed significant decreases in the total cholesterol and LDL (Nalini et al., 1999; Saravanan et al., 2007), VLDL and free fatty acid (Saravanan et al., 2007), and triglycerides (Nalini et al., 1999) in hypercholesteremic rats on treatment with TPL (Nalini et al., 1999; Saravanan et al., 2007). HDL cholesterol remained unchanged and excretion of bile acids was found to be significantly ($p < 0.01$) higher in animals receiving the TPL (Nalini et al., 1999). In another study of a randomized, double blind

Table 1. Summary of the outcomes of Triphala.

Trial design	Method and outcome	Antioxidant	title	author
<i>In vitro</i>	Antioxidant capacities of the raw fruit extracts and the major isolated substances were determined using the 1,1-diphenyl-2-picrylhydrazyl radical, oxygen radical absorbance capacity and ferric reducing ability of plasma <i>in vitro</i> assays and indicated that chebulic ellagitannins have high activity which may correlate with high potential as cancer chemopreventive agents.		Polyphenolic compounds in the fruits of Egyptian medicinal plants (<i>Terminalia bellerica</i> , <i>Terminalia chebula</i> and <i>Terminalia horrida</i>): Characterization, quantitation and determination of antioxidant capacities.	Pfundstein et al., 2010
<i>In vitro</i>	The methanol and acetone extracts exhibited good antioxidant potential than the chloroform extract.		Antioxidant activity of triphala a combination of <i>Terminalia chebula</i> , <i>Terminalia bellerica</i> and <i>Emblica officinalis</i> .	Singh et al., 2010
<i>In vitro</i>	<i>TPL</i> has been found to be an excellent scavenger of hydroxyl radicals and nitric oxide radicals, whose excessive formation is implicated in oxidative stress. <i>TPL</i> is capable of increasing the capacity to tolerate non-specific stress in experimental animals as evident from the restoration of parameters studied during different types of stress models.		Antioxidant and adaptogenic effect of an herbal preparation, Triphala.	Shivaprasad et al., 2008
<i>In vitro</i>	Alcohol extracts of <i>TPL</i> found to be strong antioxidants. The extracts also prevented lipid peroxidation induced by Fe ³⁺ /ADP/Ascorbate system in rat liver mitochondria.		Antioxidant properties of the Ayurvedic formulation Triphala and its constituents.	Vani et al., 1997
Anti hypercholesteremic				
Animal STUDY	The study highlights the efficacy of herbal formulation <i>TPL</i> on total cholesterol, LDL, VLDL, HDL and free fatty acid in experimentally induced hypercholesteremic rats.		Hypolipidemic effect of triphala in experimentally induced hypercholesteremic rats.	Saravanan et al., 2007
Randomized, double blind placebo controlled trial	Subjects and Methods: Subjects (n = 92) with mild to moderate hypercholesterolemia for a period of 12 weeks and then randomized <i>TPL</i> (6.0 g/day), and cellulose placebo (3.0 g/day).The incremental differences in triglycerides (significant) for <i>TPL</i> -6.3% with a 4.4% increase in HDL cholesterol. The incremental differences in Lipid peroxides and diene conjugates were significant for <i>TPL</i> .		Hypolipidemic and antioxidant effects of fenugreek seeds and triphala as adjuncts to dietary therapy in patients with mild to moderate hypercholesterolemia.	Singh et al.,1998
Anti-diabetic activity				
Animal STUDY	The extracts of <i>TPL</i> were given to high fructose diet fed rats, <i>TPL</i> caused a normalization of FPG. In conclusion, all three components of <i>TPL</i> showed significant anti-diabetic properties.		Anti-diabetic activity of triphala fruit extracts, individually and in combination,in a rat model of insulin resistance.	Prativadibhayankaram et al., 2008

Table 1. Contd.

Animal STUDY	<p><i>TPL</i>, that inhibited 50% of lipid peroxidation induced with Fe²⁺/ascorbate were food to be 85.5, 27, 74 and 69 mug/ml, respectively. The concentration needed for the inhibition of hydroxyl radical scavenging were 165, 71, 155.5 and 151 mug/ml, and that for superoxide scavenging activity were found to be 20.5, 40.5, 6.5 and 12.5 mug/ml, respectively. Oral administration of the extracts (100 mg/kg body weight) reduced the blood sugar level in normal and in alloxan (120 mg/kg) diabetic rats significantly within 4 hours. Continued, daily administration of the drug produced a sustained effect.</p>	Anti-diabetic activity of medicinal plants and its relationship with their antioxidant property.	Sabu et al., 2002
<i>In vitro</i>	<p style="text-align: center;">Anti-obesity</p> <p><i>TPL</i> have been reported to contain gallic acid. Gallic acid is a widely occurring phenolic compound of plant origin. Gallic acid is selected as a bioactive marker due to its easy availability, common presence in these fruits and as anti obesity property. There was significant variation in gallic acid content of fruit collected from different regions. Gallic acid was maximum in <i>Phyllanthus emblica</i> Linn.</p>	Quantitation of Gallic Acid from Fruits of <i>Phyllanthus emblica</i> Linn., <i>Terminalia bellirica</i> (Gaertn.) Roxb. and <i>Terminalia chebula</i> Retz.	Sharma et al. 2009
<i>In vitro</i>	<p style="text-align: center;">Chemopreventive potential and antimutagenic activity</p> <p>The decoctions D1 (<i>Terminalia bellerica</i>, <i>Terminalia chebula</i>, <i>Phyllanthus emblica</i> and detoxified <i>Commiphora mukul</i>) and D2 (<i>Terminalia bellerica</i>, <i>Terminalia chebula</i>, <i>Phyllanthus emblica</i>, detoxified <i>Commiphora mukul</i>, <i>Smilax china</i> and <i>Nigella sativa</i>) showed strong inhibition of cell proliferation against Rhabdomyosarcoma cells. The chemo preventive and therapeutic potential of the decoctions D1 and D2 can be explained to a certain extent by the results obtained from this study.</p>	Antioxidant and cytotoxic properties of three traditional decoctions used for the treatment of cancer in Sri Lanka.	Perera et al., 2008
<i>In vitro</i>	The MCF 7 and T 47 D cells (breast cancer cell lines) exhibited differential sensitivity to <i>TPL</i> , which seem to be dependent on their p53 status. Inhibition of anti-proliferative ability of <i>TPL</i> by antioxidants suggests a role for <i>TPL</i> induced ROS in the induction of apoptosis.	Cytotoxic response of breast cancer cell lines, MCF 7 and T 47 D to triphala and its modification by antioxidants.	Sandhya et al., 2006a
<i>In vitro and in vivo</i>	The cytotoxic effects of aqueous extract of <i>TPL</i> , were investigated on human breast cancer cell line (MCF-7) and a transplantable mouse thymic lymphoma (barcl-95). The viability of treated cells was found to decrease with the increasing concentrations of <i>TPL</i> . These results suggest that <i>TPL</i> possessed the ability to induce cytotoxicity in tumor cells but spared the normal cells.	Potential of traditional ayurvedic formulation, Triphala, as a novel anticancer drug.	Sandhya et al., 2006c
Animal STUDY	In the case of long term treatment the tumor incidences were reduced to 66.66% and 62.50% respectively by 2.5% and 5% <i>TPL</i> containing diet. Tumor burden was 7.27 +/- 1.16 in the B(a)P treated control group, whereas it reduced to 3.00 +/- 0.82 (p<0.005) by 2.5% dose and 2.33 +/- 1.03 (p<0.001) by 5% dose of <i>TPL</i> . In long-term studies the tumor burden was reduced to 2.17 +/- 0.75 (p<0.001) and 2.00 +/- 0.71 (p<0.001) by 2.5% and 5% diet of <i>TPL</i> , respectively.	Chemopreventive potential of Triphala (a composite Indian drug) on benzo(a)pyrene induced forestomach tumorigenesis in murine tumor model system.	Deep et al., 2005

Table 1. Contd.

<i>In vitro</i>	The results revealed that acetone extract of <i>TPL</i> showed a significant cytotoxic effect on these cancer cell-lines and the effect was similar on all cancer cell lines used in this study. The suppression of the growth of cancer cells in cytotoxic assays may be due to the gallic acid.	The <i>in vitro</i> cytotoxic and apoptotic activity of Triphala - an Indian herbal drug .	Kaur et al., 2005
<i>In vitro</i>	The results disclose significant inhibition of 98.7% was observed with acetone extract against the revertants induced by S9-dependent mutagen, 2-aminofluorene, in co-incubation mode of treatment.	The <i>in vitro</i> antimutagenic activity of Triphala - an Indian herbal drug.	Kaur et al., 2002
Radioprotective effect			
<i>In vitro and in vivo</i>	Protection against whole body gamma-irradiation of Swiss mice orally fed with <i>TPL</i> . It was observed in splenocytes of <i>TPL</i> fed animals that the magnitude of prevention of DNA damage was significantly higher than that observed in leukocytes. <i>TPL</i> induced protection was mediated through inhibition of oxidative damage in cells and organs.	Protection against radiation oxidative damage in mice by Triphala . Mutation	Sandhya et al., 2006c
<i>in vitro</i>	<i>in vitro</i> antioxidant activity gamma-Radiation induced strand break formation in plasmid DNA (pBR322) was effectively inhibited by <i>TPL</i> and inhibited radiation induced lipid peroxidation in rat liver microsomes effectively. Thus their mixture, <i>TPL</i> , is expected to be more efficient due to the combined activity of the individual components.	<i>In vitro</i> antioxidant studies and free radical reactions of triphala, an ayurvedic formulation and its constituents.	Naik et al., 2005a
Animal STUDY	The effects of 10 mg/kg of <i>TPL</i> extract were studied on radiation-induced sickness and mortality in mice exposed to 7-12 Gy of gamma-irradiation. However, animals in both of the <i>TPL</i> extract + irradiation and non-drug double distilled water + irradiation groups did not survive up to 30 days post-irradiation (beyond 11 Gy irradiation). The LD50/30 was found to be 8.6 Gy for the DDW + irradiation group and 9.9 Gy for TE + irradiation group. The administration of <i>TPL</i> resulted in an increase in the radiation tolerance by 1.4 Gy, and the dose reduction factor was found to be 1.15. To understand the mechanism of action of <i>TPL</i> the free radical scavenging activity of the drug was evaluated.	Triphala, an ayurvedic Rasayana drug, protects mice against radiation-induced lethality by free-radical scavenging.	Jagetia et al., 2004a
Animal STUDY	The study demonstrates the ability of <i>TPL</i> as a good radioprotective agent and the optimum protective dose of <i>TPL</i> was 1/28 of its LD50 dose.	The evaluation of the radioprotective effect of Triphala (an ayurvedic rejuvenating drug) in the mice exposed to gamma-radiation.	Jagetia et al., 2002
Immunomodulation activity			
Animal STUDY	<i>TPL</i> (1 g/kg body weight), noise-stress (100 dB/4 hr/15 days), <i>TPL</i> + noise-stress and rats were immunized with sheep red blood cells (5 x 10 ⁹) cells/ml). Results indicate that elevation in the serum antibody titer and IL-4 levels with decreased IL-2, IFN-gamma, and reduction in Pan T, CD4(+)/CD8(+) lymphocyte phenotype in spleen were significantly prevented in <i>TPL</i> treated noise-stress exposed group. And showed the immunomodulatory effect of <i>TPL</i> during noise-stress and suggests its therapeutic usefulness.	Immunomodulatory effect of Triphala during experimentally induced noise stress in albino rats.	Srikumar Ret al., 2007

Table 1. Contd.

Animal STUDY	Noise-stress employed in this study was 100 dB for 4 h/d/15 days and <i>TPL</i> was used at a dose of 1 g/kg/b.w/48 days. Results showed that noise-stress significantly suppressed the cell-mediated immune response by decreased FPT with an enhanced LMI test. The <i>TPL</i> prevents the noise- stress induced changes in the antioxidant as well as cell-mediated immune response in rats. And concludes that <i>TPL</i> restores the noise-stress induced changes may be due to its antioxidant properties.	Effect of Triphala on oxidative stress and on cell-mediated immune response against noise stress in rats.	Srikumar et al., 2006
Animal STUDY	The oral administration of <i>TPL</i> stimulate the neutrophil functions in the immunized rats and stress induced suppression in the neutrophil functions were significantly prevented by <i>TPL</i> . And noise-stress-induced changes were significantly prevented by <i>TPL</i> administration.	Immunomodulatory activity of triphala on neutrophil functions.	Srikumar et al., 2005
Clinical Trial	MMPs were extracted from gingival tissue samples from 10 patients (six males, four females) with chronic periodontitis. Tissue extracts were treated with the drug solutions, the inhibition was analyzed by gelatin zymography, and the percentage of inhibition was determined by a gel documentation system. <i>TPL</i> showed the strong inhibitory activity of <i>TPL</i> on PMN-type MMPs.	Evaluation of the inhibitory effect of triphala on PMN-type matrix metalloproteinase (MMP-9).	Abraham et al., 2005
Animal STUDY	Immunomodulatory activity was evaluated for <i>TPL</i> The experimental (On oral administration) used were cellular (foot pad swelling) immune responses to the antigenic challenge by sheep RBCs and neutrophil adhesion test, it significantly potentiated the cellular immunity by facilitating the foot pad thickness response to sheep RBCs in sensitized rats.	Immunomodulatory activity of 'triphala'	Shivaprasad et al., 2005
	Anti stress-induced		
Animal STUDY	Oral administration of <i>TPL</i> (1g/kg/animal body weight) for 48 days significantly prevented these cold stress-induced behavioral and biochemical abnormalities in albino rats. The results of this study suggest that <i>TPL</i> can be regarded as a protective drug against cold stress.	Protective effect of triphala on cold stress-induced behavioral and biochemical abnormalities in rats.	Dhanalakshmi et al., 2007
Animal STUDY	The study was aimed to investigate the antioxidant properties of <i>TPL</i> during cold-stress. Administration of <i>TPL</i> (1 g/kg/body weight/48 days) significantly prevents the cold-stress-induced oxidative stress and elevation in lipid peroxidation and corticosterone levels. This study concludes that <i>TPL</i> significantly prevents the cold-stress-induced oxidative stress may due to its antioxidant properties.	Antioxidant property of triphala on cold stress induced oxidative stress in experimental rats.	Dhanalakshmi et al., 2006
	Antimicrobial activity		
<i>In Vitro</i>	Aqueous and ethanolic extracts of <i>TPL</i> were tested against several bacteria isolates. The isolates were recovered from urethral swabs, seminal fluid, urine, high vaginal swabs, skin swabs, blood, and sputum specimen of HIV infected patients. And showed that extract of <i>TPL</i> has potent antibacterial action against the wide variety of bacterial isolates from the HIV infected patients.	Antimicrobial activity of triphala against bacterial isolates from hiv infected patients.	Amanullah et al., 2011

Table 1. Contd.

<i>In Vitro</i>	Qualitative assay with 3-week biofilm showed complete inhibition of bacterial growth with <i>TPL</i> . Qualitative assay with 6-week biofilm showed growth when treated with <i>TPL</i> .	Evaluation of Antimicrobial Efficacy of Herbal Alternatives (Triphala and Green Tea Polyphenols), MTAD, and 5% Sodium Hypochlorite against <i>Enterococcus faecalis</i> Biofilm Formed on Tooth Substrate: An <i>In Vitro</i> Study.	Prabhakar et al., 2010
<i>In vitro</i>	It inhibits the dose-dependent growth of Gram-positive and Gram-negative bacteria. In conclusion, it appears that <i>TPL</i> has non-specific antimicrobial activity.	Exploring of antimicrobial activity of Triphala Mashī - an ayurvedic formulation.	Biradar et al., 2008a
<i>In vitro</i>	The study revealed that aqueous and ethanol extracts of <i>TPL</i> have antibacterial activity against the bacterial isolates tested, by both Kirby-Bauer's disk diffusion and minimum inhibitory concentration methods.	Evaluation of the growth inhibitory activities of triphala against common bacteria isolates from HIV infected patients.	Srikumar et al., 2007
<i>In vitro</i>	The study was conducted on the antifungal/anticandidal activity of <i>TPL</i> and its ingredients. It was found that ethanolic extract of <i>TPL</i> showed outstanding anticandidal activity with lowest MIC of 3 mg/ml than the MICs of individual plant extracts.	Studies on antifungal/anticandidal activity of herbal formulation "Triphala".	Zafar et al., 2000
Anti-inflammatory			
Animal STUDY	beta-glucuronidase and lactate dehydrogenase level were reduced in <i>TPL</i> treated monosodium urate crystal-incubated polymorphonuclear leucocytes. The results obtained clearly indicated that <i>TPL</i> exerted a strong anti-inflammatory effect against gouty arthritis.	An <i>in vivo</i> and <i>in vitro</i> potential of Indian ayurvedic herbal formulation Triphala on experimental gouty arthritis in mice.	Sabina et al., 2008
Animal STUDY	The evaluation the antiarthritic effect of the <i>TPL</i> on adjuvant-induced arthritis in mice and to compare it with that of the non-steroidal anti-inflammatory drug indomethacin. The results obtained clearly indicate the fact that the <i>TPL</i> has promising anti-inflammatory activity.	Antiinflammatory effect of the Indian ayurvedic herbal formulation triphala on adjuvant-induced arthritis in mice.	Rasool et al., 2000
Wound healing			
Animal STUDY	HPLC analysis showed the presence of (-) epigallocatechin gallate. FT-IR spectroscopy study revealed the interaction of polyphenols with the collagen. <i>TPL</i> dressing has shown to increase thermal stability and water uptake capability, faster wound closure, improved tissue regeneration, collagen content at the wound site, and supporting histopathological parameters pertaining to wound healing. Better healing efficacy of <i>TPL</i> may provides a scientific rationale for the use of this dressing as an effective wound cover in the management of infected dermal wound.	Triphala Incorporated Collagen Sponge-A Smart Biomaterial for Infected Dermal Wound Healing	Kumar et al., 2010
Animal STUDY	An ointment was prepared from the <i>TPL</i> extract (10% w/w) and assessed for <i>in vivo</i> wound healing on infected rat model by rate of healing. Assessment of granulation tissue showed significant reduction in bacterial count with significant level of collagen, hexosamine, uronic acid, and superoxide dismutase in the treated group (P < 0.01). The above results showed the antibacterial, wound healing, and antioxidant activities of <i>TPL</i> ointment, necessary for the management of infected wounds.	Triphala promotes healing of infected full-thickness dermal wound.	Kumar et al., 2008

Table 1. Contd.

	Enteroprotective efficacies		
Animal STUDY	<p><i>TPL</i> formulations were prepared by mixing equal and unequal proportions. Intestinal damage was induced by administering MTX in a dose of 12 mg/kg, orally for 4 days to albino rats. The intestinal damage response was assessed by gross and microscopical injury, measuring the intestinal permeability to phenol red and tissue biochemical parameters. <i>TPL</i> equal and unequal formulations at the dose of 540 mg/kg significantly restored the depleted protein level in brush border membrane of intestine, phospholipid and glutathione content and decreased the myeloperoxidase and xanthine oxidase level in intestinal mucosa of MTX -treated rats. <i>TPL</i> unequal formulation provides significantly more protection than <i>TPL</i> equal formulation.</p>	Comparison of Enteroprotective Efficacy of Triphala Formulations (Indian Herbal Drug) on Methotrexate-Induced Small Intestinal Damage in Rats.	Nariya et al., 2009
	Anti- diarrhoeal		
Animal STUDY	<p>The remarkable anti-diarrhoeal effect of <i>TPL</i> extracts against castor oil-induced diarrhoea suggest its potential for application in a wide range of diarrhoeal states.</p>	Evaluation of Anti-Diarrhoeal Property and Acute Toxicity of Triphala Mashi, an Ayurvedic Formulation.	Biradaret al., 2008b
	Nitric oxide scavenging activity		
<i>In vitro</i>	<p>The results suggest that the traditional polyherbal crude drugs may be potent and novel therapeutic agents for scavenging of NO.</p>	evaluation of nitric oxide scavenging activity of certain herbal formulations <i>in vitro</i> : A preliminary study.	Jagetia et al., 2004b
	Anti gastric ulcers activity		
<i>In vitro</i>	<p>The polyherbal formulation NR-ANX-C [(composed of the extracts from <i>Withania somnifera</i>, <i>Camellia sinensis</i>, <i>Ocimum sanctum</i>, shilajith and <i>TPL</i>) (25 and 50 mg/kg)] was more efficacious than ranitidine in reducing ulcer index in both the models. At the highest dose tested, NR-ANX-C was comparable to omeprazole in preventing ulcer formation in the pyloric ligature model. NR-ANX-C showed a dose-dependent decrease in gastric juice volume and total acidity in both the models. A dose-dependent increase in gastric pH and total adherent gastric mucus was also seen in NR-ANX-C treated groups. The extent of lipid peroxidation was also reduced in the test drug treated groups.</p>	Evaluation of the anti-ulcer activity of NR-ANX-C (a polyherbal formulation) in aspirin & pyloric ligature induced gastric ulcers in albino rats.	Nair et al., 2010
	Alleviate catalepsy		
Animal STUDY	<p>In the study we evaluated the anticataleptic efficacy of NR-ANX-C, in haloperidol induced catalepsy in mice. Significant (P<0.01) reduction in the cataleptic scores was observed in all NR-ANX-C treated groups and maximum reduction was observed in the NR-ANX-C (25 mg/kg) treated group. Significant (P<0.05) reduction in SOD activity was observed in NR-ANX-C (25 and 50 mg/kg) treated groups and maximum reduction was observed in NR-ANX-C (25mg/kg) treated group.</p>	Effect of NR-ANX-C (a polyherbal formulation) on haloperidol induced catalepsy in albino mice.	Nair et al., 2007

Table 1. Contd.

Correcting menstrual irregularities			
open clinical trial-	This was studied on 50 women, suffering from menstrual irregularities, in an open, prospective clinical study. The drug was administered through oral route at a dose of 10 ml b.i.d. for 90 days. Majority of the subjects 61.54% with increased duration of cycles showed mean reduction of days from baseline to end of the study. The trial drug was also found to be effective in reducing the increased flow, which was clinically significant. All the subjects failing under both irregular cycle duration and irregular bleeding days reflected relief from the respective clinical symptoms. The study reveals that the preparation could be effective in correcting menstrual irregularities.	open clinical trial to evaluate the efficacy of a herbal preparation for menstrual irregularities.	Chaudhari et al., 2006
Clinical trial	Effect of laxative and antihyperacidity and improve appetite <i>TPL</i> was found to have good laxative properties, helped in the management of hyperacidity and also improve appetite. No adverse effect was observed in the treated group when compared to normal patients. <i>TPL</i> can be used effectively in the treatment of constipation and other gastric problems.	Clinical study of 'TRIPHALA' – A well known phytomedicine from india.	Mukherjee et al., 2006
<i>TPL</i> mouthwash in prevention of dental caries			
Clinical trial	The study was conducted on 1501 students with the aim of determining the effect of <i>TPL</i> mouthwash on prevention of dental caries, and also comparing with chlorhexidine mouthwashes. The incipient caries was recorded at 3, 6, 9 months intervals. No significant increase in the DMFS scores was found at the end of 9 months. It was concluded that there was no significant difference between the <i>TPL</i> and the chlorhexidine mouthwashes.	Effect of <i>Triphala</i> mouthwash on the caries status.	Tandon et al., 2010
Anticataract potential of <i>Triphala</i>			
<i>In vitro</i> and <i>in vivo</i>	The study was undertaken to evaluate its anticataract potential <i>in vitro</i> and <i>in vivo</i> in a selenite-induced experimental model of cataract. <i>In vivo</i> selenite cataract was induced in rat pups by subcutaneous injection of sodium selenite. At the end of the study <i>TPL</i> significantly ($P < 0.01$) restored glutathione and decreased malondialdehyde levels. A significant restoration in the activities of antioxidant enzymes such as superoxide dismutase ($P < 0.05$), catalase ($P < 0.05$), glutathione peroxidase ($P < 0.05$), and glutathione-s-transferase ($P < 0.005$) was observed in the <i>TPL</i> group compared to controls. <i>In vivo</i> <i>TPL</i> 25mg/kg developed only 20% nuclear cataract as compared to 100% in control. <i>TPL</i> prevents or retards experimental selenite-induced cataract.	Evaluation of anticataract potential of <i>Triphala</i> in selenite-induced cataract: <i>In vitro</i> and <i>in vivo</i> studies.	Gupta et al., 2010
<i>In vitro</i>	Dose of 1080 mg of <i>TPL</i> ghrita offered significant protection against delaying the onset and progression of cataract in comparison to other doses. This effect may be attributed to the antioxidant activity of gallic acid, ellagic acid and ascorbic acid which shows their presence in <i>TPL</i> ghrita.	Investigation on Anticataract Activity of <i>Triphala</i> Ghrita	Mahajan et al., 2011

Abbreviations: FPT: foot pad thickness; LMI: leukocyte migration inhibition; HD :hyper cholesterolemia diet; FPG:fasting plasma glucose; MIC: minimum inhibitory concentration; MTX: methotrexate.

placebo controlled trial showed that the LDL/HDL cholesterol ratio significantly declined; fasting and postprandial blood glucose as well as lipid peroxides and diene conjugates (indicators of oxidative stress) significantly decreased in the TPL group whereas these changes were not significant in the placebo group; and the results also showed antioxidant effects (Singh et al., 1998).

Anti-diabetic activity

Some studies have investigated the possible anti-diabetic properties of combination TPL in animal models (Prativadibhayankaram et al., 2008; Sabu et al., 2002), one in a high fructose diet induced (Prativadibhayankaram et al., 2008) and another in alloxan diabetic rats. The results of these studies show that the administration of the extracts reduced the blood sugar level (Prativadibhayankaram et al., 2008; Sabu et al., 2002). They were found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals *in vitro* (Prativadibhayankaram et al., 2008).

Anti-obesity

One study which evaluated the herbal formulation TPL in mice showed that the body weight was found to be reduced when compared with the control animals (Rasool et al., 2000). Gallic acid is a phenolic compound of TPL which is selected as a bioactive marker due to its easy availability, and its anti-obesity property (Sharma et al., 2009).

In our view, sufficient clinical data are available to qualify certain TPL preparations for the category of well-established medicinal products, fulfilling the requirements for well-established use defined in the assessment of clinical safety and efficacy in the preparation of TPL for well-established entries to the list for traditional herbal medicinal products, substances, and preparations. Accordingly, a randomized, double-blind, placebo-controlled, clinical safety and efficacy trial at Shahed University in collaboration with Endocrinology and Metabolism Research Institute (EMRI) has been conducted for evaluation of the activity of TPL in obesity implementation (unpublished data).

Chemo-preventive potential and anti-mutagenic activity

Many studies showed that TPL is useful in the prevention of cancer and possesses anti-neoplastic, radio-protective and chemo-protective properties (Arora et al., 2003, 2005; Baliga., 2010; Deep et al., 2005; Kaur et al., 2002, 2005; Sandhya et al., 2006a, c; Shi et al., 2008; Perera et

al., 2008). The aqueous extract, induced apoptosis in Capan-2 cells and in pancreatic cancer cell. And reduced tumor-growth in TPL fed mice. On the other hand, TPL failed to induce apoptosis or activate extracellular signal-regulated kinase (ERK) or phosphorylation of p53 (p53) in normal human pancreatic ductal epithelial (HPDE-6) cells (Shi et al., 2008). TPL was found to induce apoptosis in MCF-7 and barcl-95 cells *in vitro*. Treated MCF-7 and barcl-95 cells had significant increase in intracellular reactive oxygen species (ROS). The differential effect of TPL on normal and tumor cells seems to be related to its ability to evoke differential responses in intracellular ROS generation. This effect suggests potential use as an anticancer drug for clinical treatment (Sandhya et al., 2006c). The anti-proliferative ability by antioxidants suggests a role for TPL induced ROS in the induction of apoptosis and also significantly increased the antioxidant status of animals which might have contributed to the hemoprevention (Sandhya et al., 2006a).

One study has shown that TPL in diet has significantly reduced the benzo(a)pyrene induced fore-stomach papillomagenesis in mice. Moreover, TPL was effective in reducing tumor incidences (Deep et al., 2005). The suppression of the growth of cancer cells may be due to the gallic acid (Kaur et al., 2005). All the extracts were found to have potent antimutagenic effects against the direct acting mutagens 4-nitro-o-phenylenediamine, sodium azide, S9-dependent mutagen, and 2-aminofluorene (2AF) (Arora et al., 2005). Antimutagenic activities of the extracts were more effective against indirect acting mutagen, than against the direct acting mutagens (Arora et al., 2003). In addition a significant inhibition of 98.7% was observed with acetone extract against the revertants induced by S9-dependent mutagen, 2AF, in co-incubation mode of treatment (Kaur et al., 2002). Also, strong inhibition of cell proliferation against rhabdomyosarcoma cells has been shown (Perera et al., 2008).

Radioprotective effect

The radioprotective effect of TPL have been shown in many studies (Naik et al., 2005a; Jagetia et al., 2004a, 2002; Sandhya et al., 2006c). In one of these studies, aqueous extract was studied on the radiation-induced mortality.

The treatment of mice with different doses before irradiation delayed the onset of mortality and reduced the symptoms of radiation sickness. 10 mg/kg TPL intraperitoneally (i.p) was found to provide the best protection as evidenced by the highest number of survivors after 30 days post-irradiation. The LD50 i. p. dose of TPL was found to be 280 mg/kg. This study demonstrated the ability of TPL as a good radioprotective agent and the optimum protective dose of TPL was 1/28

of its LD50 dose (Jagetia et al., 2002).

Immunomodulatory activity

Many studies have assessed the immunomodulatory effects of TPL on stress (Abraham et al., 2005; Shivaprasad et al., 2005, 2006; Srikumar et al., 2005, 2006, 2007). Stress results in immuno dysfunction (Srikumar et al., 2007). Neutrophil functions were significantly enhanced in the TPL immunized group and a significant decrease in corticosterone level was observed (Srikumar et al., 2005). According to the results of these trials, stress significantly increased the lipid peroxidation (LPO) and corticosterone level with concomitant depletion of antioxidants in plasma and tissues (Srikumar et al., 2006). One study on noise-stress in male albino rats indicated that elevation in the serum antibody titer and IL-4 levels associated with decreased IL-2, IFN-gamma, and reduction in Pan T, CD4(+)/CD8(+) lymphocyte phenotype in the spleen were significantly prevented in TPL treated noise-stress exposed group (Srikumar et al., 2007). Another study evaluated the inhibitory activity of TPL on PMN-type matrix metalloproteinase (MMP-9) expressed in adult periodontitis patients. This study showed a 76.6% reduction of MMP-9 activity (Abraham et al., 2005) and 'TPL' showed a significant increase in neutrophil adhesion and delayed type hypersensitivity response (Shivaprasad et al., 2005).

Miscellaneous activities

Antimicrobial activity

Many studies have been conducted on TPL that are effective against multiple human pathogens (Amarasingha et al., 2007; Biradar et al., 2008a; Madani et al., 2008; Zafar et al., 2000; Mehrotra et al., 2010; Nageeb et al., 2010; Prabhakar et al., 2010; Srikumar et al., 2007; Sumathi and Parvathi, 2010), and also showed significant antibacterial activity against 32 different strains of *Salmonella typhi* (Sumathi and Parvathi, 2010).

Anti-inflammatory

Several studies have evaluated the antiarthritic effect of TPL (Prabhakar et al., 2010; Rasool et al., 2000). One study indicated that gallic acid is a selective inhibitor of COX-2. Being a small natural product with selective and reversible inhibition of COX-2, gallic acid would form a lead molecule for developing potent anti-inflammatory drug (Prabhakar et al., 2010). TPL treatment significantly inhibited the levels of lysosomal enzymes, LPO and inflammatory mediator tumor necrosis factor-alpha;

however the anti-oxidant status was found to have increased in plasma, liver and spleen (Sabina et al., 2008).

Wound healing

TPL has shown *in vitro* wound healing activity (Kumar et al., 2008, 2010). In one study, an infected wound was dressed with TPL (methanol extract). The study revealed that matrix metalloproteinases expression was correlated well with reduction in the inflammatory phase, thus confirming efficacy of the dressing (Kumar et al., 2010). Another study showed *in vitro* activity against wound pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. Reduction of matrix MMP expression was observed in the treated group by gelatin zymography (Kumar et al., 2008).

Enteroprotective efficacies and anti-diarrheal

The enteroprotective efficacies, examined the comparative against methotrexate-induced intestinal damage in rats. This study showed that TPL unequal formulation provides significantly more protection than TPL equal formulation (Nariya et al., 2009). The anti-diarrheal effects of aqueous and alcoholic extracts of TPL were studied employing castor oil-induced-diarrheal model in rats. These studies showed that TPL has remarkable anti-diarrheal effects (Biradaret al., 2008b).

Nitric oxide scavenging activity

Various polyherbal drugs exhibited dose-dependent NO scavenging activities and thereby inhibit the pathological conditions caused by excessive generation of NO and its oxidation product and peroxynitrite. These findings revealed pharmacological activities like rejuvenating, adaptogenic, anti-infection, anti-inflammatory, cardioprotective and neuroprotective activities of these traditional and clinically used non toxic drugs (Jagetia et al., 2004b).

Anti gastric ulcers activity and alleviate catalepsy

The evaluated anti-ulcer efficacy of the polyherbal formulation NR-ANX-C (composed of the extracts from *Withania somnifera*, *Camellia sinensis*, *Ocimum sanctum*, shilajith and TPL) presume that the cytoprotective, anti-secretory and antioxidant properties of NR-ANX-C were responsible for its anti-ulcer activity (Nair et al., 2010). In one study, catalepsy was induced by intraperitoneally administration of haloperidol, and degree of catalepsy (cataleptic score) was measured as the time the animal maintained an imposed posture. The study compared the anticataleptic efficacy of NR-ANX-C with scopolamine.

The SOD level in brain tissue was also estimated to be correlated with the levels of oxidative stress and degree of catalepsy in the animal. Findings suggest antioxidant potential of NR-ANX-C in alleviating haloperidol induced catalepsy (Nair et al., 2007).

DISCUSSION

TPL consists of the three myrobalans, *T. chebula* (Haritaki), *T. belerica* (Bibhitaki), and *P. emblica* or *Emblica officinalis* (Amalaki or the Indian gooseberry) (Baliga, 2010). The formulation generally contained of equal proportions of wall of a fruit of these myrobalans (Ibn-e-sina, 2005). Phytochemical analysis of TPL is rich in phenols/polyphenols ($38 \pm 3\%$) and tannins ($35 \pm 3\%$) (Arora et al., 2003; Naik et al., 2006), while flavonoids were found to be absent (Naik et al., 2006). High-pressure liquid chromatography (HPLC) analysis showed the presence of compounds such as ascorbate (Naik et al., 2004; Pawar et al., 2009), and ellagic acid (Naik et al., 2004, Prativadibhayankaram et al., 2008), chebulagic acid and chebulinic (Pawar et al., 2009; Luo et al., 2011), mucic acid, 1,4-lactone 3-O-gallate, isocorilagin, mallotusin were isolated and purified from this plant (Luo et al., 2011). Availability of many nutrient elements such as Mg, Ca, K, Fe, and Se in TPL (Garg et al., 2005) and powder was rich in Cr, Fe, Se and Zn, whereas the tablet contained a four-fold higher Mn compared to the powder (Choudhury et al., 2007). In addition, efficient separation of gallic acid has been showed in some trials (Naik et al., 2004; Pawar et al., 2009; Garg et al., 2005; Jadon et al., 2007). HPLC analysis showed that it contains 73 ± 5 mg gallic acid per gram of triphala (Naik et al., 2006) and gallic acid as the major component (Kaur et al., 2005). The choice of the solvent system toluene-ethyl acetate-formic acid is discussed and its utility is demonstrated for complete resolution of gallic acid from other components. Gallic acid therefore can be used as a marker compound for standardizing TPL (Bahulikar et al., 2003). Gallic acid may be useful in quality control and standardization of several herbal formulations and crude drugs containing phenolics and tannins (Ahmad et al., 2011). These analyses showed tannic acid, syringic acid and epicatechin along with ascorbic acid (Garg et al., 2005). The major phenolic compounds of the alcohol extracts were confirmed as tannins (Vani et al., 1997).

Accumulation of heavy metals including arsenic content in herbal formulations is below the permissible limit in all formulations. The lead content is below detectable level in all formulations (Bais et al., 2011). Besides, aqueous and alcoholic extracts of TPL were considered safe up to a dose of 1750 mg/kg when evaluated for acute oral toxicity in accordance with the Organization for Economic Cooperation and Development guidelines (Biradar et al., 2008b) and clinically used non toxic drugs (Dhanalakshmi et al., 2006).

Some of the experimental studies have shown that the mechanisms responsible for the many effects of TPL such as increase in antioxidant enzymes (Sandhya et al., 2006b), increase in free radical scavenging activity (Jagetia et al., 2004b), selective apoptosis, superoxidized dimutase(SOD), catalase (Deep et al., 2005), glutathione (Deep et al., 2005), decrease in oxidative stress, lipid peroxidation (Naik et al., 2005a), inflammation (Rasool et al., 2000), lactate dehydrogenase and xanthine oxidase (Sandhya et al., 2006b).

Conclusion

It is important for us, in medicine, to recognize that many of the traditional formulation contain healing potentials. TPL has shown itself to be one of these herbal combinations. This herbal combination can have profound healing benefits in multi-organ systems and exhibits a number of health benefits like antioxidant activity, anti hyperlipidemia, reducing tumors in animals and so on. TPL is rich in Mg, K, Ca, Fe, Se and Zn, and the presence of gallic acid and polyphenols enhance their bioavailability (Jadon et al., 2007). Studies indicate that TPL may be a potent and novel therapeutic agent for scavenging of NO, and thereby inhibit the pathological conditions caused by excessive generation of NO and its oxidation product and peroxynitrite. These findings may also help to explain, at least in part, the pharmacological activities like rejuvenating, adaptogenic, anti-infection, anti-inflammatory, cardioprotective and neuroprotective activities of this traditional, and clinically used non toxic drug (Pinmai et al., 2008). Since, free radicals have been implicated in the causation of several diseases such as liver cirrhosis, atherosclerosis, cancer, and diabetes, it is obvious that this mixture which could scavenge free radicals have great potential in improving these disease processes (Wilson, 1998).

Trials to validate the experimentally observed of many effects of TPL need to be performed, as then the efficacy will be clearly understood. Further pharmacological evidences at molecular level are required to establish the mechanism of the action of this polyherbal medicine.

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