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Review of the Phytochemical, Pharmacological and Toxicological Properties of *Punica granatum* L., (Lythraceae) Plant

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Abstract

Pomegranate is considered as "wonder fruit" because of its various therapeutic effects. This paper aims to provide an up-to-date overview of the phytochemical, pharmacological and toxicological properties. The research strategy includes review of the existing literature in the ISI Web of Knowledge (Thomson Reuters), textbooks and Pharmacopeias from year 1978 to 2016. Phytochemical screening shows that its fruit, juice, seeds, flowers, leaves, root, bark and fruit peel contains the following; gallic acid, ellagic acid, punicalin, punicalagin, caffeic acid, citric acid, malic acid, succinic acid, tartaric acid, acetic acid, oxalic acid, shikimik acid, maleic acid, furamic acid ellagitannins, pelletierine alkaloids, piperidine alkaloid, isopelletierine, methyl-pelletierine, pseudopelletierine, glucoside, granatic acid, luteolin, kaempferol, quercitin, catechin, EGCG, rutin, flavones, flavonones, flavonoid,flavonols, steroids, lignins, fats & oils, cardiac glycosides, carbohydrates, anthocyanidins, anthocyanins melatonin, delfinidin 3-O-glucoside, punicacortein A, punicacortein B, pedunculagin, tellimagrandin, glucose, delphinidin, gallagyldilacton, tannins, simple sugars, aliphatic organic acids, quinic acid, amino acids, minerals, ascorbic acids, ursolic acid, triterpinoids, fatty acids, 3,3'-Di-O-methylellagic acid ; 3,3',4'- Tri-O-methyellagic acid, punicic acid, oleic acid, palmitic acid, stearic acid, linoleic acid, sterols, tocopherols, sex steroids and other coloring matter. Moreover, pharmacological properties includes antiatherosclerotic, antimicrobial, antidiabetic, anti-inflammatory, analgesic, antidiarrheal, antimutagenic, antioxidant, antiparasitic, antiviral, astringent, abortifacient, hemorrhoids, cancer-chemopreventive, improve fertility, neuronal activity, gastroprotective, hepatoprotective, nephroprotective, and skin whitening activity. In toxicological assessment, ten patients with carotid artery stenosis demonstrated that juice consumption (121 mg/ LEA equivalents) for up to three years had no toxic effect on the blood chemistry analysis for kidney, liver and heart function. Human trials were also conducted using doses of pomegranate fruit extracts up to 1,420 mg/day (870mg gallic acid equivalents), for 28 days and did not report any adverse changes in blood or urine laboratory values. The methanolic extract of peel exhibited no significant toxicity (LC50 = 1.42 mg/ml) against *Artemia salina* (brine shrimp). For the whole fruit, animal studies have failed to report any toxicities at doses conventionally used in the conventional system of medicine. The overall finding of the review suggests that *Punica granatum* whole fruit is safe up to 2000 mg/kg body weight oral administration and can be considered as non-toxic. Therefore, based on the review conducted it shows that *Punica granatum* is a promising herbal plant that can be developed into a suitable pharmaceutical dosage form.

Keywords

Phytoconstituents, Pharmacological, Toxicological, *Punica granatum* L.

1. Introduction

Punica granatum L., (Lythraceae) plant has various medicinal properties in all parts of the plant and this is due to the phytoconstituents present in the plant. This paper aims to provide an up-to-date overview of the phytochemical, pharmacological and toxicological properties. The research strategy includes review of the existing literature in the ISI Web of Knowledge (Thomson Reuters), textbooks and Pharmacopeias from year 1978 to 2016 using terms 'pomegranate' or *Punica granatum*. Citations relevant to the topic were screened. Below is the tabulated phytoconstituents distributed throughout the plants found by various researchers around the world.

Table 1 Phytoconstituents found in different parts of the plants

Plant Parts	Phytconstituents Found	References
Pomegranate peel	Gallic acid, Ellagic acid, Punicalin, Punicalagin, Caffeic acid, Ellagitannins, Pelletierine alkaloids, Luteolin, Kaempferol, Quercitin, Catechin, EGCG, Rutin, Flavones, Flavonones, Flavonoid,Steroids, Lignins, Fats & Oils, Cardiac glycosides, Carbohydrates, Anthocyanidins, Melatonin, Delfinidin 3-O-glucoside, Punicacortein A, Punicacortein B, Pedunculagin, Tellimagrandin, Glucose, Delphinidin, Gallagyldilacton, Tannins and other coloring matter	Quisumbing, E. 1978 Tanaka T, et al, 1986 Neuhofer H, et al 1993 Nawwar MA et al, 1994 Artik N. 1998 Amakura Y et al, 2000 de Pascual-Teresa S et al, 2000 Gil MI., et al, 2000 Machado, T.B. et al, 2002 Noda Y et al, 2002 Vidal A., et al, 2003 Philippine Pharmacopeia 1, 2004 van Elswijk, DA. 2004 Jurenka, J. 2008 Mali, A.B. et al, 2011 Rajan, S. et al, 2011 Anibal, P.C., et al, 2013 Moghaddam, G. et al, 2013 Altunkaya, A. 2014 Foss, S.R. et al, 2014 Sadeghipour, A. et al, 2014 Haque, N., et al, 2015
Pomegranate juice	Simple sugars, Aliphatic organic acids, Gallic acid, Ellagic acid, Quinic acid, Flavonols, Amino acids, Minerals, Ascorbic acid, Anthocyanins, Caffeic acid, Catechin, Epigallocatechin gallate (EGCG), Quercetin, Rutin, Citric acid, Malic acid, Succinic acid, Tartaric acid, Acetic acid, Oxalic acid, Shikimik acid, Maleic acid, Furamic acid	Du Ct et al, 1975 Artik N. 1998 Amakura Y et al, 2000 de Pascual-Teresa S et al, 2000 Poyrazoglu, E., et al., 2002 Cui, S.M., et al, 2004 Waheed S et al, 2004 Lansky EP, & Newman RA. 2007 Aarabi, A., 2008 Jurenka, J. 2008 Bhandari, P. 2015 Sadeghipour, A. et al, 2014
Pomegranate root and bark	Ellagitannins, Including Punicalin and Punicalagin, Piperidine alkaloid, Pelletierine alkaloids, Isopelletierine, Methyl-pelletierine, Pseudopelletierine, Glucoside, Granatic acid, Gallic acid, Tannic acid	Quisumbing, E. 1978 Tanaka T, et al, 1986 Neuhofer H, et al 1993 Tripathi, S.M. & Singh, D.K. 2000 Jurenka, J. 2008 Sadeghipour, A. et al, 2014

Pomegranate flower	Gallic acids, Ursolic acid, Triterpinoids, Fatty acids	Batt AK and Rangaswami S. 1973 Huang TH et al, 2005 Jurenka, J. 2008 Sadeghipour, A. et al, 2014
Pomegranate leaves	Carbohydrates, Reducing sugars, Sterols, Saponins, Flavonoids, Tannins (punicalin and punicafolin), Piperidine alakloids, Flavone Glycoside, Ellagitannins, Luteolin and Apigenin	Tanaka T, et al, 1986 Nawwar MA et al, 1994 Gil MI., et al, 2000 Jurenka, J. 2008 Chaitra, R.H. et al., 2012 Sadeghipour, A. et al, 2014 Haque, N. et al, 2015
Pomegranade seeds	3,3'-Di-O-methylellagic acid ; 3,3',4'-Tri-O-methyellagic acid, Punicic acid, Oleic acid, Palmitic acid, Stearic acid, Linoleic acid, Sterols, Tocopherols, Sex steroids	Schubert SY et al, 1999 Abd El Wahab SM et al, 1998 Amakura Y et al, 2000 Hornung, E. et al, 2002 Wang, RF. Et al, 2004 Jurenka, J. 2008 Altunkaya, A. 2014 Sadeghipour, A. et al, 2014 Bhandari, P. 2015 Haque, N. et al, 2015

The above phytoconsituents were responsible for the pharmacological activities of this plant. Below are the tabulated therapeutic and toxicological findings of different plant parts conducted by various researchers.

Table 2 Pharmacological studies conducted in different parts of the plant

Pharmacological Studies	Plant Part Used	Findings
Antiatherosclerotic	Pomegranate juice	Daily consumption of pomegranate juice improves stress-induced myocardial ischemia in patients who have Coronary Heart Disease. Sumner, M.D. et al, 2005 ; Bhandari, P.R. 2015 Has a beneficial effect on the evolution of clinical vascular complications, coronary heart disease, and other atherogenesis in humans, by enhancing the NOSIII bioactivity. de Nigris, F. et al, 2006 ; Bhandari, P.R. 2015 Consumption of concentrated pomegranate juice - a significant decrease was seen in total cholesterol (P<0.006), low-density lipoprotein-cholesterol (LDL-c) (P<0.006), LDL-c / high density lipoprotein-cholesterol (HDL-c) (P<0.001), and total cholesterol / HDL-c (P<0.001). Esmaillzadeh, A., et al., 2006 : Bhandari, P.R. 2015 Juice consumption by diabetic patient resulted in anti-oxidative effects on the serum and macrophages, which could contribute to the attenuation of atherosclerosis development in these patients. Rosenblat, M. et al, 2006 ; Bhandari, P.R. 2015 Results suggested that in subjects who were at risk for moderate coronary heart disease, pomegranate juice consumption had no significant effect on the overall carotid intima-media thickness (CIMT) progression rate, but may have slowed CIMT progression in subjects with increased oxidative stress and disturbances in the TG-rich lipoprotein / HDL axis. Davidson, M.H et al 2009 ; Bhandari, P.R. 2015

		Cardioprotective Basu A. et al 2009 ; Bhandari, P.R. 2015 Juice consumption lowers blood pressure and good for cardiovascular health. Stowe, CB 2011 ; Bhandari, P.R. 2015
	Pomegranate flower	Its extract diminishes cardiac fibrosis in Zucker diabetic fatty rats, at least in part, by modulating cardiac ET-1 and NF-kappaB signaling. Huang, T.H. et al, 2005 ; Bhandari, P.R. 2015
	Pomegranate seeds	Administration of seed oil for four weeks in hyperlipidemic subjects had encouraging effects on lipid profiles, including TAG and the TAG:HDL-C ratio. Mirmiran, P., et al, 2010 ; Bhandari, P.R. 2015
Antibacterial/Antifungal Activity	Pomegranate juice	Adjunctive local delivery of extract from *Centella asiatica*, in combination with pomegranate, significantly improved the clinical signs of chronic periodontitis and IL-1 beta level in maintenance patients (P<0.006). Sastravaha, G., 2005 ; Bhandari, P.R. 2015 Has antibacterial activity against dental plaque microorganisms. Menezes, S.M. et al, 2006 ; Bhandari, P.R. 2015 Ethanolic extract of fruit presented an MICs of 500 ug/mL to *C. albicans*, 250 ug/mL to *C. dubliniensis*, 500 ug/mL to *C. tropicalis*, 250 ug/mL to *C. krusei*, 250 ug/mL to *C.guilliermondii*, 500 ug/mL to *C. utilis*, 125 ug/mL *C. parapsilosis*, 125 ug/mL to *C. lusitaniae*, 250 ug/mL to *C. glabrata* and 250 ug/mL to *C. rugosa* compared to Nistatin. Anibal, P.C et al, 2013 Drinking its juice shows antibacterial properties against harmful bacteria that can exist in the stomach such as *Escherichia coli* and *Bacillus subtilis* (Bhowmilk, D. et al, 2013).
	Pomegranate peel (pericarp, rind)	Dysentery. Quisumbing, E. 1978 Traditional uses----- A decoction of the dried pericarp is used in the treatment of diarrhea and dysentery. Externally used as gargle in cases of sore throats. Philippine Pharmacopeia 2004 The MICs of adherence of *Punica granatum* L. gel (peel extract) against the test organisms were 1:16 for *Streptococcus mutans* (ATCC), *S. mutans* (CI) and *S. sanguis*; 1:128 for *S. mitis* and 1:64 for *C. albicans*. The MICs of adherence of micronazole against the same organisms were: 1:512, 1:64, 1:4, 1:128 and 1:16 (de Souza Vasconcelos, L.C. et al, 2006). Potent antifungal activity of extracts and pure compound isolated from pomegranate peels and synergism with fluconazole against *C. albicans* (Endo, EH. 2010) Efficacious against the *Aggregatibacter actinomycetemcomitans*, *Pophyromonas gingivalis*, and *Prevotella intermedia* strain *in vitro* Bhadbade, S.J. et al, 2011 ; Bhandari, P.R. 2015 Extracts of pomegranate and *Juglans regia* have remarkable anti-*H.pylori* activity, with a mean of inhibition zone diame-

		ter of 39 and 16 mm at 100ug disk. Hajiimahmoodi, M. et al, 2011; Bhandari, P.R. 2015 Ethanolic extract showed greater zone of inhibition (mm) against Tetracycline. *Staphylococcus aureus* (25 vs. 23), *Escherichia coli* (22 vs. 19) and *Pseudomonas aeruginosa* (25 vs. 21). Khan, J.A. et al, 2011 Ethanolic extract of pericarp presented an MICs of 125 ug/mL to *C. albicans*, 125 ug/mL to *C. dubliniensis*, 250 ug/mL to *C. tropicalis*, 125 ug/mL to *C. krusei*, 125 ug/mL to *C.guilliermondii*, 62.5 ug/mL to C. utilis, 31.5 ug/mL *C. parapsilosis*, 62.5 ug/mL to *C. lusitaniae*, 62.5 ug/mL to *C. glabrata* and 125 ug/mL to *C. rugosa* compared to Nistatin (Anibal, P.C et al, 2013). Methanolic extract of peel inhibited growth of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus* compared to ciprofloxacin (Rummun, N. et al, 2013) The hydroalcoholic extract showed good activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa* with MICs of 62.5, 62.5 and 250 ug/mL ; *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis* and *Microsporum gypseum* with MICs of 125 ug/mL and 250ug/mL respectively for each genus (Foss, S.R. et all 2014).
	Pomegranate flower	Bronchitis and as gargles Quisumbing, E. 1978 Methanolic extract of peel inhibited growth of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus* compared to ciprofloxacin (Rummun, N. et al, 2013)
	Pomegranate leaves	Gargles for affections of buccal cavity and as an eyewash Qusiumbing, E. 1978 Methanolic extract of peel inhibited growth of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus* compared to ciprofloxacin (Rummun, N. et al, 2013)
	Pomegranate stem	Methanolic extract of peel inhibited growth of *Streptococcus mutans*, *Streptococcus mitis*, and *Lactobacillus acidophilus* compared to ciprofloxacin (Rummun, N. et al, 2013)
	Pomegranate root	Against tuberculosis disease of children Quisumbing, E. 1978
Antidiabetic	Pomegranate flower	Its extract has antidiabetic activity due to improved sensitivity of the insulin receptor. Huang, T.H. 2005 ; Bhandari, P.R. 2015
Antiinflammatory	Pomegranate juice	Dietary supplementation is a useful complementary strategy to attenuate clinical symptoms in rheumatoid arthritis patients. Balbir-Gurman, A., et al, 2011; Bhandari, P.R. 2015
	Pomegranate peel	Dietary supplementation with ellagitannins, may mitigate muscular damage experienced after eccentric exercise, producing delayed-onset of muscle soreness. Supplementation with ellagitannins significantly improves the recovery of isometric strength two to three days after a damaging eccentric exercise. Trombold, J.R., et al, 2010 ; Bhandari, P.R. 2015 The aqueous-ethanolic (50%) extracts of fruit rind at 500 mg/Kg p.o. inhibited inflammation by 82.14% against indo-

		methacin (79%) at 10mg/Kg (Bagri, P. et al, 2010). An aqueous pomegranate peel extracts inhibits neutrophil myeloperoxidase *in vitro* and attenuates lung inflammation in mice (Bachoual, R. et al, 2011).
	Pomegranate flower	The aqueous-ethanolic (50%) extracts of flower at 500 mg/Kg p.o. inhibited inflammation by 71.42% against indomethacin (79%) at 10mg/Kg (Bagri, P. et al, 2010).
	Pomegranate leaves	The aqueous-ethanolic (50%) extracts of leaves at 500 mg/Kg p.o. inhibited inflammation by 67.85% against indomethacin (79%) at 10mg/Kg (Bagri, P. et al, 2010).
Analgesic Activity	Pomegranate peel	Has 77.61% of analgesia compared to indomethacin (59.49%) Bagri, P. et al, 2010.
	Pomegranate flower	Has 54.05% of analgesia compared to indomethacin (59.49%) Bagri, P. et al, 2010.
	Pomegranate leaves	Has 50.35% of analgesia compared to indomethacin (59.49%) Bagri, P. et al, 2010.
Antidiarrheal	Pomegranate peel	The anti-diarrheal activity of aqueous and alcohol extract of the fruit rind of pomegranate was investigated in three experimental models, using albino rats. The extract exhibited significant activity in rats, when compared to loperamide hydrochloride, a standard anti-diarrheal drug. Pillai, N.R. et al, 1992 ; Bhandari, P. 2015
Antimutagenic	Pomegranate peel	Broad spectrum antimutagenic activity of antioxidant active fraction of *Punica granatum* L. peel extracts (Zahin, M. et al 2010).
Antioxidant	Pomegranate peel	Aqueous and alcoholic extracts showed good antioxidants effect with IC_{50} ranges from 34.78 $\pm$ 14.04 to 135.27 $\pm$ 35.5 ug/mL for aqueous and 40.03 $\pm$ 14.72 to 105.93 $\pm$ 17.19 ug/mL for alcoholic extracts (Rajan, S. et al, 2011).
	Pomegranate flower	Potent antioxidant Kaur, G. et al, 2006 ; Bhandari, P. 2015
Antiparasitic	Pomegranate juice	Infected women who accepted to be treated with pomegranate juice were completely cured. The anti-trichomoniasis vaginalis activity of extract (*in-vitro* and *in-vivo*) gave very promising results. El-Sherbini, G.M. et al, 2010 ; Bhandari, P. 2015
	Pomegranate peel	Internally as decoction for antihelminthic and taeniafuge Quisumbing, E. 1978 Anthelminthic against tapeworm and other intestinal worms. Philippine Pharmacopeia 2004
	Pomegranate bark	For tapeworm Quisumbing, E. 1978 Molluscicidal activity Tripathi, S.M. et al, 2000 ; Bhandari, P. 2015
Antiviral activity	Pomegranate juice	Microbiocidal effects on HIV-1 Neurath, A.R. 2005 ; Bhandari, P. 2015 Viricidal agent De Siqueira,R.S. et al, 2006 ; Bhandari, P. 2015 Has an anti-influenza component, because this compound blocked the replication of the virus RNA, inhibited agglutination of chicken RBCs by the virus, and had viricidal effects. Indeed, it inhibited the replication of human influenza A/Hong Kong (H3N2) in vitro. Haidari, M., et al, 2009 ; Bhandari, P. 2015

Abortifacient	Pomegranate peel	Abortifacient, Philippine Pharmacopeia 2004
Astringent	Pomegranate juice	Fruit extract in a range of 5 to 60 mg/L, is able to protect human skin fibroblasts from cell death on UV exposure, possibly due to a decrease in induction of the pro-inflammatory transcription factor NF-kappaB, a downregulation of pro-apoptotic caspase-3, and an increased G0/G1 phase, associated with DNA repair. Results from this study demonstrate the protective effects of pomegranate fruit extract against UVA-and UVB-induced cell damage and the potential use of pomegranate polyphenolics in topical applications Pacheco-Palencia, L.A. et al, 2008 ; Bhandari, P. 2015
	Pomegranate peel	Astringent, Philippine Pharmacopeia 2004
Cancer-chemopreventive	Pomegranate juice	Prevents prostate cancer in humans. Malik, A. et al, 2005 ; Bhandari, P. 2015 Results suggest that the ellagitannins and urolithins liberated in the colon, upon administration of pomegranate juice, in considerable amounts, could potentially reduce the risk of colon cancer progress, by inhibiting cell proliferation and inducing apoptosis. Kasimsetty, SG., et al, 2010 ; Bhandari, P. 2015 It sensitizes Tamoxifen action in ER-α positive breast cancer cells. Banerjee, S. et al, 2011 ; Bhandari, P. 2015 It inhibits cellular proliferation and tumor growth and induce cell death via apoptosis in a number of cancer cell lines (leukemias). Dahlawi, H. et al, 2012 ; Bhandari, P. 2015
	Pomegranate seeds	Punicic acid in seed oil had breast cancer inhibitor properties due to its effect on lipid peroxidation and the PKC pathway. Grossmann, M.E. et al, 2010;Bhandari, P. 2015 Has protective effect toward the liver and kidney by reducing the level of lipid peroxidation in patients receiving chemotherapy medications like Cisplatin. Cayir, K., et al, 2011 ; Bhandari, P. 2015
Fertility	Pomegranate juice	A well-controlled trial of pomegranate juice for the treatment of mild-to-moderate erectile dysfunction in men, was made by Forest CP et al, 2007. The randomized, placebo-controlled, double-blind, crossover trial, enrolled 53 men with mild-to-moderate impotence. The subjects consumed pomegranate juice, or placebo, for four weeks. After a two-week washout period, they switched treatments. They concluded that the subjects were more likely to have improved scores when pomegranate juice was consumed. Bhandari, P. 2015 Juice consumption increased the epididymal sperm concentration, sperm motility, spermatogenic cell density, diameter of seminiferous tubules, and germinal cell layer thickness. It also decreased the abnormal sperm rate when compared to the control group. Turk, G., et al, 2008 ; Bhandari, P. 2015
Gastroprotective	Pomegranate juice	Anti-ulcer activity in experimentally-induced gastric ulcers. Alam, M.S., et al, 2010 ; Bhandari, P. 2015 Its antiulcer effect is related to the increasing secretion of adherent mucus and free mucus from the stomach wall. This

		may inhibit generation of oxygen-derived free radicals, decrease the consumption of GSH-PX (glutathione peroxidase) and SOD (superoxide dismutase), and maintain the content of NO (Nitric Oxide) at a normal level. Lai, S. et al, 2009 ; Bhandari, P. 2015
Hepatoprotective	Pomegranate peel	It prevents liver firbrosis in biliary-obstructed rats. Toklu, H.Z. 2007 ; Bhandari, R. 2015
	Pomegranate flower	Hepatoprotective Kaur, G. et al, 2006 ; Bhandari, P. 2015 Ameliorates diabetes and obesity-associated fatty liver, at least in part, by activating the hepatic expression of genes responsible for fatty acid oxidation. Xu, K.Z. et al, 2009 ; Bhandari, P. 2015
Hemorrhoids	Pomegranate peel	Hemorrhoids, Philippine Pharmacopeia 2004
Nephroprotective	Pomegranate seeds	Nephroprotective Bouroshaki, M.T. et al,2010 ; Bhandari, P. 2015
Neuronal activity	Pomegranate flower	Supplementation decreases oxidative stress and ameliorates impairment in learning and memory performances in diabetic rats. Cambay, Z., et al, 2011 ; Bhandari, P. 2015
Skin whitening activity	Pomegranate juice	Ingested orally, has an inhibitory effect on pigmentation in the human skin caused by UV irradiation Bae, J.Y. et al, 2010 ; Bhandari, P. 2015
	Pomegranate peel	It's extract when taken orally, could be used as an effective whitening agent for the skin Yoshimura, M. et al, 2005 ; Bhandari, P. 2015
Toxicity Testing / Safety	Pomegranate whole fruit	Animal studies have failed to report any toxicities at doses conventionally used in the conventional system of medicine. Vidal, A. et al, 2003 ; Bhandari, P. 2015 Ten patients with carotid artery stenosis demonstrated that juice consumption (121 mg/ LEA equivalents) for up to three years had no toxic effect on the blood chemistry analysis for kidney, liver and heart function. Aviram, M., et al, 2004 ; Bhandari, P. 2015 Human trials using doses of pomegranate fruit extracts up to 1,420 mg/day (870mg gallic acid equivalents), for 28 days, did not report any adverse changes in blood or urine laboratory values. Heber, D. et al, 2007 ; Bhandari, P. 2015 There were no behavioral alterations or mortality recorded in the treated groups. The LD50 value was more than 2000 mg/kg body weight. Test groups did not record any significant alterations ($p>0.05$) in body weight gain, food and water intake. The hematological and biochemical parameters and organ weights did not record any significant alterations ($p>0.05$) in the treated groups when compared to control. A detailed examination of histoarchitecture of the liver and kidney did not reveal any observable cellular damage in the treated groups compared to control. Conclusion: The overall finding of this study suggests that *Punica granatum* (L) whole fruit (EPWF) and seeds (EPS) ethanolic extract and synthetic ellagic acid (EA) is safe up to 2000 mg/kg body weight oral administration and can be considered as non toxic. Satheesh Kumar Bhandary, B., et al, 2013
	Pomegranate peel	Repeated oral administration of high doses of the pomegran-

		ate ellagitannin punicalagin to rats for 37 days is not toxic. Cerda, B. et al, 2003 ; Bhandari, P. 2015 The methanolic extract of peel exhibited no significant toxicity (LC50 = 1.42 mg/ml) against *Artemia salina* (brine shrimp). Mehru, N., et al, 2008 Repeated doses including 0.5, 1.9 and 7.5 mg/Kg body weight of pomegranate peel extract were gavaged to BALB/c mice, for 22 days and the single intradermal injection (224 mg/Kg) was done in single dose. In addition intra dermal injection for skin allergy testing was also performed. Studies revealed no toxic effects, clinical signs, histopathological effect in epithelial cells layer of tongue, larynx and trachea, behavioral alterations and adverse effects or mortality in BALB/c mice. Repeated administration did not alter or cause local irritation of the oral mucosa. Skin allergy test was negative. Jahromi, S.B., et al, 2015 In the acute toxicity studies of oral administration of the aqueous peel extract, phenols, alkaloids and terpenoid crude extract of *Punica granatum* none of the animals showed behavioral, neurological or physical changes. In addition, no mortality was observed at the test dose. The median lethal dose (LD50) of the plant extract was found to be greater than 2000 mg/Kg. Ibrahim, O.M. S. and Shwaysh, M.M., 2016
	Pomegranate seeds	There were no behavioral alterations or mortality recorded in the treated groups. The LD50 value was more than 2000 mg/kg body weight. Test groups did not record any significant alterations ($p>0.05$) in body weight gain, food and water intake. The hematological and biochemical parameters and organ weights did not record any significant alterations ($p>0.05$) in the treated groups when compared to control. A detailed examination of histoarchitecture of the liver and kidney did not reveal any observable cellular damage in the treated groups compared to control. Conclusion: The overall finding of this study suggests that *Punica granatum* (L) whole fruit (EPWF) and seeds (EPS) ethanolic extract and synthetic ellagic acid (EA) is safe up to 2000 NBAZmg/kg body weight oral administration and can be considered as non toxic. Satheesh Kumar Bhandary, B., et al, 2013

Summary

Punica granatum L., (Lythraceae) is rich in phytoconstituents that are distributed to its different plant parts such as fruits, seeds, leaves, flowers, bark, roots, fruit peel and juice. These phytoconstituents were responsible for the pharmacological properties exhibited namely antiatherosclerotic, antimicrobial, antidiabetic, anti-inflammatory, analgesic, antidiarrheal, antimutagenic, antioxidant, antiparasitic, antiviral, astringent, abortifacient, hemorrhoids, cancer-chemopreventive, improve fertility, neuronal activity, gastroprotective, hepatoprotective, nephroprotective, and skin whitening activity. As for toxicological assessment the overall finding of this study suggests that *Punica granatum* L., whole fruit (EPWF) and seeds (EPS) ethanolic extract and synthetic ellagic acid (EA) is safe up to 2000 NBAZ mg/kg body weight oral administration and can be considered as non-toxic ND.

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