

Active Constituents of Pomegranates (*Punica granatum*) as Potential Candidates in the Management of Health through Modulation of Biological Activities

Arshad Husain Rahmani, Mohamed Ali Alsahli, Saleh Abdulrahman Almatroodi

ABSTRACT

Pomegranates fruits have innumerable health benefits and its implication in diseases cure have been widely recognized since ancient time. Moreover, pomegranate fruits, seeds and peels are intensively used in traditional medicine as a natural therapy. It contains numerous valuable ingredients such as flavonoids, ellagitannin, punicalagin, ellagic acid, vitamins and minerals. The principal constituents including punicalagins and ellagitannin are responsible for immeasurable health benefits due to its strong antioxidant activity. Additionally, constituents of pomegranate show health promoting effect through the modulation of physiological and biochemical pathways. Recent evidences suggested that pomegranates fruits, peels and seeds illustrate therapeutics implications in health management via inhibition of free radical effect and modulation of enzymes activity linked with diseases development and progression. In this review, we summarize the therapeutic role of pomegranate fruits, seeds and peels in the health managements based on *in vitro* and *in vivo* studies.

Key words: Pomegranates, Anti-oxidant, Anti-inflammatory effect, Hepatoprotective effect, Neuroprotective effect and anti-microbial effects.

INTRODUCTION

Plants and their products are commonly used in the cure of diseases since ancient time. Recent study demonstrated that medicinal plant shows therapeutic role in disease management through the modulation of biological activities.^{1,2} Recent finding based on *in vitro* and *in vivo* suggested that pomegranate has health-promoting effects mainly attributed due to its polyphenol content/antioxidant activity.

However, its health promoting effect has also been mentioned in the traditional medicines. Fruits, seeds, peel and leaves of pomegranate contain various types of valuable ingredients and such ingredients show therapeutics role in the disease cure. Pomegranate peel is a rich source of tannins, flavonoids and other phenolic compounds.³ Its juice also contains various constituents such as polyphenols, tannins, anthocyanins, including vitamin C, vitamin E, and lipoic acid⁴ and punicalagin bioactive constituent responsible for more than 50% of the antioxidant activity of pomegranate juice.⁵ Pomegranate fruits, peels and seeds have proven its role in diseases cure via modulation of biological activities. Earlier investigators demonstrated that pomegranate extract exhibited scavenging activity against hydroxyl (OH) and superoxide.⁶ Consumption of pomegranate extract potently delayed the onset and reduced the incidence of collagen-induced arthritis and severity of arthritis was significantly lower in pomegranate extract fed animals.⁷ In this review, we

summarize the therapeutic role of pomegranate in the diseases managements based on *in vitro* and *in vivo* studies.

Chief Constituents of Pomegranate

Pomegranate fruits hold various types of constituents in different parts such as seeds, peels and arils. Such ingredients show therapeutic role in the health management through the modulation of various biological activities. Peels of the pomegranate covers around 60% of the fruit and they hold various types of ingredients including flavonoids, ellagitannins and proanthocyanidin compounds and minerals such as calcium, magnesium, phosphorus, potassium and sodium.⁸

Pomegranate fruit arils contain huge amounts of organic acids, sugars, minerals, vitamins, and polyphenols that show antioxidant effect.⁹ Moreover, flavonoids are chief polyphenols of fruit, condensed tannins and hydrolysable tannins.¹⁰⁻¹² Hydrolyzable tannins including ellagitannins and gallotannins consist of the common constituents present in pomegranate, and punicalagin is the major hydrolyzable tannin present in pomegranates.¹³⁻¹⁶ The juice of arils consist of water, sugars such as glucose, sucrose, and fructose,¹⁷ 1.5% pectin, organic acids including citric, malic, tartaric, succinic, fumaric and ascorbic acid.¹⁸ Pills also have hydroxybenzoic

Arshad Husain Rahmani,
Mohamed Ali Alsahli,
Saleh Abdulrahman Almatroodi

Departments of Medical Laboratories
College of Applied Medical Sciences,
Qassim University, SAUDI ARABIA.

Correspondence

Dr. Arshad Husain Rahmani, Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University, SAUDI ARABIA.

Phone no: 00966-16-3800050-Ext. 4835.

E-mail: rehmani.arshad@gmail.com

History

- Submission Date: 29-05-2017;
- Review completed: 20-06-2017;
- Accepted Date: 03-07-2017

DOI : 10.5530/pj.2017.5.109

Article Available online

<http://www.phcogj.com/v9/i5>

Copyright

© 2017 Phcog.Net. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license.



Cite this article : Rahmani AH, Alsahli MA, Almatroodi SA. Active Constituents of Pomegranates (*Punica granatum*) as Potential Candidates in the Management of Health through Modulation of Biological Activities. Pharmacogn J. 2017;9(5):689-95.

acids such as gallic acid, ellagic acid and EA glycosides.¹⁹ Additionally, seeds hold constituents such as protein, crude fibers, vitamins, minerals, sugars, polyphenols, the phytoestrogen coumestrol estrone.²⁰⁻²³

Pharmacological Activities of Pomegranate

Antioxidant Activity

Medicinal plants make their importance in health managements through antioxidant activity and inhibition of free radical effects. Antioxidant activities of plants have been proven by earlier studies.²⁴⁻²⁶ Pomegranate shows antioxidant activity due to abundance of compounds such as flavonoids, flavones, anthocyanins and catechins in different parts including fruits, seeds and peels [Table 1]. Experiment was made to explore the antioxidant activity of pomegranate peels and seeds result of the confirmed that extract of peels and extract of seeds showed antioxidant activity. Furthermore, methanol extract of peel demonstrated highest antioxidant activity among all of the tested extracts.²⁷ Another study revealed that pretreatment of extract of peel followed by treatment of CCL₄ showed preservation of enzymes including catalase, peroxidase, and SOD. Additionally, lipid peroxidation was brought back by 54% as compared to control.²⁸

The antioxidant activity of pomegranate peel powder and whey powder was evaluated and results showed that peel powder and whey powder exhibited antioxidant activity.²⁹ Other previous report demonstrated that leaf and peel exhibited very strong antioxidant activity³⁰ and extracts obtained from seeds exhibited various degrees of antioxidant activity and sour white peel had the highest potent antioxidant activity.³¹

Anti-Inflammatory and Analgesic Effect

Non-steroidal anti-inflammatory agents are effective in the cure of inflammation. Non-steroidal anti-inflammatory based treatment exhibit adverse effect through the inhibition of arachidonic acid metabolism. However, treatments based on natural products are very effective in the cure of inflammation without any severe adverse effect on the arachidonic acid metabolism and cyclo-oxygenase enzyme activity. Several studies finding confirmed that pomegranate has role in the reduction of inflammation by modulation of various physiological activities [Table 1]. Anti-inflammatory and analgesic activities of fruit rind, flower, and leaves was measured and it was observed that pretreatment with the dried extracts produced significant and dose dependent inhibition of edema when compared to the control groups.³² Topical anti-inflammatory and analgesic activities of a standardized pomegranate rind extract of which ellagic acid (EA) was assessed and finding reported that rind extract and the equivalent ellagic acid dose-dependently reduced the ear edema. Furthermore, Both rind extract and ellagic acid showed significant topical analgesic activities in the rat punctuate mechanical hyperalgesia test and in the mouse formalin test.³³ Indomethacin-induced gastric injury was not observed in the presence of pomegranate, which also prove role in the protection against ethanol-induced gastric lesions³⁴ and pomegranate methanolic extract exhibited potent analgesic and anti-inflammatory activity comparable to indomethacin.³⁵ Wound healing activity of a rind extract and ellagic acid was investigated. Outcome of the study showed both rind extract and its equivalent amount of ellagic acid increased the tensile strength of the incision wound.³⁶ Pomegranate extract and urolithin-A decreased inflammation markers (iNOS, cyclooxygenase-2, PTGES and PGE (2) in colonic mucosa) and modulated favorably the gut microbiota.³⁷

Other study finding revealed that pomegranate fruit extract inhibited the IL-1beta-induced proteoglycan breakdown in cartilage explants. In addition, extract also inhibited the IL-1beta-induced phosphorylation of IkkappaBalpha and the DNA binding activity of the transcription factor NF-kappaB in OA chondrocytes.³⁸ Consumption of dietary supplements

containing pomegranate extract potentially delayed the onset and reduced the incidence of collagen-induced arthritis and severity of arthritis was significantly lower in extract fed animals.⁵

Hepatoprotective Effect

Numerous plants including curcumin, green tea, dates fruits and ginger or plant based formulation shows very effective role in the prevention of liver damage and diseases related to liver. Investigators demonstrated that rats fed on diets supplemented with pomegranate peel powder, whey powder or their mixture showed a potential hepatoprotective effects compared to liver injury control group²⁶ and feeding of rats with pomegranates powder show protective effect against carbon tetra chloride toxicity.³⁹ The effect of chronic administration of pomegranate peel extract on liver fibrosis was examined and results confirmed that plasma AOC and hepatic GSH levels were considerably depressed by bile duct ligation whereas increased back to control levels in the peel extract-treated bile duct ligation group.⁴⁰

Effect on Reproductive System

Several medicinal plants have established their role in reproductive system through the elevation of hormones and maintenance of spermatogenesis. In this concern, pomegranate also shows pivotal role in the elevation of hormones linked to reproductive system [Table 2]. Study results revealed that pomegranate juice showed elevation in testosterone, luteinizing hormone and follicle stimulating hormone depleted after the injection of carbon tetra chloride (CCL₄). Moreover, result also demonstrated that degeneration of germ and Leydig cells along with deformities in spermatogenesis due to the CCL₄ injections were restored with the treatment of pomegranate juice.⁴¹ Another finding confirmed that extract and ascorbic acid administration reduced the deleterious effect of lead acetate on daily sperm production and epididymal sperm number.⁴² Experiment was made to examine the effects of pomegranate juice consumption on sperm quality, spermatogenic cell density. Outcome of the study confirmed that juice consumption showed increase in epididymal sperm concentration, sperm motility and spermatogenic cell density.⁴³ Long-term pomegranate juice intake increased intracavernous blood flow, improved erectile response and smooth muscle relaxation in erectile dysfunction.⁴⁴

Anti-Diabetic Activity

A range of studies evidences that medicinal plants or constituents of medicinal plants show role in the management of diabetes and its complication including Diabetic retinopathy.

Ethanol extract of leaves showed noteworthy antidiabetic activity and it is also found to be highly effective in managing the complications associated with diabetes mellitus.⁴⁵ Another research was carried out to investigate the anti-diabetic, hypolipidemic and antioxidant activity and study results concluded that fruit peel and LPG has shown anti-diabetic and hypoglycemic activity.⁴⁶

Administration of crude powder of *Punica granatum* husk decreased the concentration of glucose, triglycerides, cholesterol, LDL cholesterol and raised the level of HDL cholesterol and hemoglobin content in the blood of normal group and alloxan diabetic group treated rats.⁴⁷ Study finding revealed that seed and rind extracts showed significant reduction in the rise in blood glucose.⁴⁸

Anti-Microbial Activity

Antibiotics are effective remedy in the inhibition of bacteria growth or growth of microorganism. On the other side, antibiotics resistance against microorganism is one of the major problems in the use of antibiotics against microorganism. Plants products or ingredients of seeds,

flowers, stem, bark and leaves show very effective role in the inhibition of growth of pathogens. Plants are one of the good sources of secondary metabolites including tannins, terpenoids, alkaloids, flavonoids and glycosides, which confirmed antimicrobial activities *in vivo*.^{49,50} In this phenomenon, *Punica granatum* shows a very effective role in the inhibition of microorganism growth [Table 3].

Anti-Bacterial Activity

Previous study based on pomegranate peel reported that peel has antibacterial effect.⁵¹ Antimicrobial activity against some food-borne pathogens via various extracts of fruit peels was examined and finding confirmed that methanolic extract of peels was a potent inhibitor for *Listeria monocytogenes*, *S. aureus*, *Escherichia coli* and *Yersinia enterocolitica*.⁵² *In vitro* antibacterial activities of different extracts of fruit peels and arils were evaluated against food-related bacteria. Finding of the study showed that all pomegranate extracts contained high levels of phenolics and exhibited antibacterial activity against all bacteria tested.⁵³ Extracts of pomegranate such as aqueous and methanolic demonstrated that good antibacterial activity against *S. aureus* and *P. aeruginosa*.⁵⁴

Anti-Viral Activity

Earlier investigators demonstrated that tannin from the pericarp is a very effective constituent against genital herpes virus (HSV-2) and effectively kills virus and block its absorption to cells.⁵⁵ Other finding reported that acidity of juice and liquid extract solutions contributed to rapid anti-influenza activity.⁵⁶

Anti-Fungal Activity

Antifungal activities of pomegranate peel extract, seed extract, juice and whole fruit evaluated. Results confirmed that among the selected bacterial and fungal cultures, the highest antibacterial activity was noticed against *Staphylococcus aureus* and among fungi high activity was observed against *Aspergillus niger*.⁵⁷ Data obtained in research with substances of *Punica granatum* established that antimicrobial capacity against yeast cells of *Candida* genus.⁵⁸

Anti-Plasmodium Activity

Gallagic acid and punicalagins showed anti-plasmodial activity against *Plasmodium falciparum* D6 and W2 clones.⁵⁹ The protective role of pomegranate peel extract against plasmodium chabaudi-induced spleen tissue damage was evaluated. Finding revealed that treated mice with pomegranate significantly showed reduction in parasitemia compared to untreated control.⁶⁰ Another earlier study concluded that beneficial effect of the fruit rind for the treatment of malarial disease might be attributed to the anti-parasitic activity.⁶¹

Anti-Diarrheal Effects

Experiment was performed to evaluate the anti-diarrheal effects of the aqueous extract of peels and finding demonstrated that extract exhibited a concentration-dependent inhibition of the spontaneous movement of the isolated rat ileum and attenuated acetylcholine-induced contractions.⁶²

Photo-Protection Activity

Chronic UVA exposure can damage underlying structures in the dermis and cause premature photoaging of the skin.⁶³ Evidences based on research demonstrated that pomegranate shows photo-protection activity [Table 2]. Previous finding revealed that pomegranate seed oil was shown to stimulate keratinocyte proliferation in monolayer culture. Furthermore, a mild thickening of the epidermis was observed in skin organ culture.⁶⁴

Other findings revealed that pomegranate extract showed effective at protecting human skin fibroblasts from cell death after UV exposure.⁶⁵

Pretreatment of epiderm with pomegranate-derived products showed inhibition of UVB-induced cyclobutane pyrimidine dimers.⁶⁶

Anti-Obesity Effect

Obesity is one of the risk factor for various diseases. Research was carried out to check the anti-obesity effects of the pomegranate leaf extract And study finding demonstrated that extract showed a significant decrease in body weight, energy intake and various adipose pad weight percents and serum, TC, TG, glucose levels.⁶⁷

Effect on Oral Health

Pomegranate juice is effective against dental plaque microorganisms decreasing the CFU. Additionally, there was significant reduction in the level of dental plaque microorganisms after the rinsing with pomegranate juice.⁶⁸

Effect of the hydroalcoholic extract from fruits on dental plaque microorganisms was evaluated and finding showed that extract was effective against dental plaque microorganisms. Another research was performed to examine young adults for the effects of mouth rinsing with the pomegranate extract PomElla[®] and this treatment changed salivary measures relevant to oral health including gingivitis.⁷⁰

Effect on Cardiovascular Diseases

Recent study based on pomegranates reported that pomegranates and its constituents shows various types activities including antioxidant, anti-inflammatory, anti-diabetic and in cardiovascular health.⁷¹ Chronic administration of pomegranate juice extract showed reduction in the

Table 1: Antioxidant and anti-inflammatory properties of pomegranate

Plant Part	Activity	Outcome/Findings of the study	Ref.
Peels	Antioxidant	Pretreatment of the rats with the methanolic extract of peel showed preservation of catalase, peroxidase, and SOD to values comparable with control values.	27
Seeds	Antioxidant	Seeds extract showed antioxidant activity.	27
Leaves, peel, seeds, and juice	Antioxidant	Leaf and peel exhibited very strong antioxidant activity.	30
Seed	Antioxidant	Pomegranate seeds extract using various solvents exhibited various degrees of antioxidant activity.	31
Fruit rind, flower and leaves	Anti-inflammatory and analgesic	Oral pretreatment with the dried extracts of <i>P. granatum</i> produced statistically significant and dose dependent inhibition of edema induced when compared to the control groups.	32
Rind	Anti-inflammatory and analgesic	Standardized pomegranate rind extract and the equivalent EA dose-dependently reduced the croton oil-induced mouse ear edema.	33
Fruits	Anti-inflammatory	Both PE and UROA decreased inflammation markers (iNOS, cyclooxygenase-2, PTGES and PGE (2)).	37

Table 2: Role of pomegranate in health management

Plant Part/extract	Activity/effect	Outcome/Findings of the study	Ref.
Peel powder	Hepatoprotective	Diets supplemented with 10% PPP, 10% WP or 10% of their mixture (PPWP) showed a potential hepatoprotective effects in rats.	29
Juice	Hormone elevation	Juice showed elevation in testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) those depleted by the injection of CCl ₄ .	41
Ethanol extract	Prevention of spermatogenic disruption	Ethanol extract of pomegranate prevented LA-induced spermatogenic disruption in rats.	42
Juice	Enhancement of sperm motility	Juice consumption showed increase in epididymal sperm concentration, sperm motility and spermatogenic cell density.	43
Juice	Improvement of erectile dysfunction	Long-term pomegranate juice intake increased intracavernous blood flow, improved erectile response	44
Leaves	Antidiabetic	Ethanol extract of leaves showed noteworthy antidiabetic activity.	45
Leaves and Fruit peel extract	Anti-diabetic, hypolipidemic and antioxidant	Leaves and fruit peel extract of <i>P. granatum</i> possesses significant anti-diabetic, hypolipidemic and antioxidant properties.	46
Seed and rind extract	Anti-diabetic	Seed and rind extract showed reduction the rise in blood glucose induced by alloxan, with the rind extract exhibiting significantly better activity than seed extract.	48
Peels extract	Anti-diarrheal	Peels extract caused a dose-dependent decrease of gastrointestinal transit and markedly protected rats against castor oil-induced diarrhea enteropooling.	61
Pomegranate extract	Skin health management	Pomegranate extract showed effective at protecting human skin fibroblasts from cell death following UV exposure.	65
Pomegranate-derived products	Skin health management	Pretreatment of epiderm with pomegranate-derived products resulted in inhibition of UVB-induced; collagenase gelatinase, stromelysin, marilysin, elastase and tropoelastin.	66
Leaf extract	Anti-obesity	Leaf extract-treated groups showed a significant decrease in body weight, energy intake and various adipose pad weight percents	67
Juice	Oral health management	Pomegranate juice is effective against dental plaque microorganisms	68
Fruit extract	Oral health management	Hydroalcoholic extract was effective against dental plaque microorganisms	69
Juice extract	Cardiovascular complications management	Juice extract showed reduction in the mean arterial blood pressure and vascular reactivity changes to various catecholamines	70
Juice	Cardiovascular complications management	Juice can exert beneficial effects on the evolution of clinical vascular complications, coronary heart disease	73
Pomegranate supplementation	Neuro-protection	Membrane-bound enzymes were altered in the brain regions of Tg2576 mouse treated with control diet, and pomegranate supplementation restore the activities of enzymes to comparable values noticed in the controls.	77
Fruit peel	Nephrotoxicity protection	Fruit peel administration showed a noteworthy amelioration of abnormalities related Cd-nephrotoxicity	80
Flower extract	Nephrotoxicity protection	Flower extract has protective role and ameliorate nephrotoxicity induced by gentamicin	81

mean arterial blood pressure and vascular reactivity changes to various catecholamines.⁷²

Other findings reported that pomegranate juice consumption decreased LDL susceptibility to aggregation and retention and increased the activity of serum paraoxonase.⁷³ Study research suggests that pomegranate juice exert beneficial effects on the evolution of clinical vascular complications, coronary heart disease, and atherogenesis in humans.⁷⁴ Consumption of pomegranate juice hold anti-atherosclerotic properties which might be associated to its powerful anti-oxidative characteristics.⁷⁵

Another study revealed that where ten patients were supplemented with pomegranate juice for 1 year and five of them continued for up to 3 years. Control group that did not take pomegranate juice, common carotid intima-media thickness (IMT) increased by 9% during 1 year, while, pomegranate juice consumption resulted in a significant IMT reduction after 1 year.⁷⁶

Neuro-Protective Effect

Prior results reported that pomegranate juice extracts has neurotoxicity protective effect in primary human neurons in a dose-dependent manner by attenuating MPTP-induced increase in extracellular LDH activity.⁷⁷ Membrane-bound enzymes were altered in the brain regions of Tg2576 mouse treated with control diet, and 4% pomegranate supplementation restore the activities of enzymes to comparable values noticed in the controls.⁷⁸ Experiment was made to examine the effects of ellagic acid in a rat model of parkinson's disease and results reported that right medial forebrain bundle MFB-lesioned rats showed hyperalgesic responses to the stimulus in tail-flick and hot-plate tests and memory and learning deficit in cognitive tests.⁷⁹

Nephro-Protective Effect

Extracts of pomegranate, mainly methanol peel extract is an effective nephro-protective agent on chronic renal failure.⁸⁰ Fruit peel admin-

Table 3: Anti-microbial activities

Plant Part	Activity	Outcome/Findings of the study	Ref.
Peel	Antibacterial	Zones of inhibition were significantly higher in pomegranates extract as compared to standard antibiotic discs used	51
Peel	Antibacterial	methanolic extract of peels was a potent inhibitor for <i>Listeriamonocytogenes</i> , <i>S. aureus</i> , <i>Escherichia coli</i> and <i>Yersinia enterocolitica</i> .	52
Peels and arils	Antibacterial	Pomegranate extracts exhibited antibacterial activity against all bacteria tested.	53
Fruit skin	Antibacterial	Extracts showed good antibacterial activity against <i>S. aureus</i> and <i>P. aeruginosa</i> .	54
Pericarp	Anti-viral	Tannin from the pericarp is a very effective constituent against genital herpes virus (HSV-2)	55
Juice (PJ), concentrated liquid extract (POMxl), and PP powder extract (POMxp)	Anti-viral	Acidity of PJ and POMxl solutions contributed to rapid anti-influenza activity.	56
Peel, seed, juice and whole fruit	Antifungal	Antifungal activity of different part of pomegranates was noticed with different potentiality.	57
Arils and seeds, pericarp, peels and whole fruit	Antifungal	Pericarp and peel showed activity against <i>Candida</i> spp	58
Peel	Antimalaria	Treated mice with pomegranate significantly showed reduction in parasitemia as compared to untreated control.	60
Fruit rind	Anti parasitic	The beneficial effect of the fruit rind for the treatment of malarial disease may be attributed to the anti-parasitic activity.	61

istration showed a noteworthy amelioration of abnormalities related Cd-nephrotoxicity and enhanced the detoxification process in mice⁸¹ and other finding concluded that pomegranates extract has protective role and ameliorate nephrotoxicity induced by gentamicin.⁸²

Anti-Tumor Activity

Cancer is multi-factorial diseases and numerous factors involve in this process. In this vista, pomegranates fruits, seed and peels illustrate cancer preventive role seems to be due to rich source of antioxidants. The effects of an extract of pomegranate (PE) on a mouse mammary cancer cell line WA4 were investigated. It was noticed that extract showed the inhibition of the proliferation of WA4 cells in a time- and concentration dependent manner.⁸³ Chemopreventive efficacy of pomegranate fruit extract and diallyl sulfide alone and in combination was investigated. Results revealed that fruit extract and diallyl sulfide alone delayed onset and tumor incidence by around 55% and around 45%, respectively, whereas their combination synergistically decreased tumor incidence more potentially at low doses.⁸⁴ Earlier investigators demonstrated that apoptotic cell numbers were significantly increased and the pro-apoptotic gene Bax expression was increased, and anti-apoptotic gene Bcl-2 was decreased after extract treatment.⁸⁵

CONCLUSION

The health promoting effect of pomegranates has also been mentioned in the traditional medicines. Fruits, seeds, peel and leaves of pomegranate contain numerous important ingredients and such ingredients show therapeutics importance in the disease cure. A large number of evidences based on laboratory research revealed that pomegranates shows effective role in diseases cure through the modulation of numerous biological activities. The allopath-based treatment including non-steroidal anti-inflammatory is expensive and also shows toxic effect on normal cells. Several studies based on animal model and clinical trials confirmed that the consumption of pomegranate is safe and not causes any side effects. However, more studies based on animal model should be warranted to explore its beneficial effect in health management.

ACKNOWLEDGMENT

The authors are thankful to Department of Medical Laboratories, Qassim University, Saudi Arabia for providing the facility to design this work.

CONFLICT OF INTEREST

There is no conflict of interest.

ABBREVIATION USED

AO: Antioxidant capacity; **EA:** Ellagic acid; **PJ:** Pomegranate juice; **MPTP:** 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **SOD:** Superoxide dismutase; **GSH:** Glutathione Inducible nitric oxide synthase; **iNOS** **CCL4:** Carbon Tetra chloride.

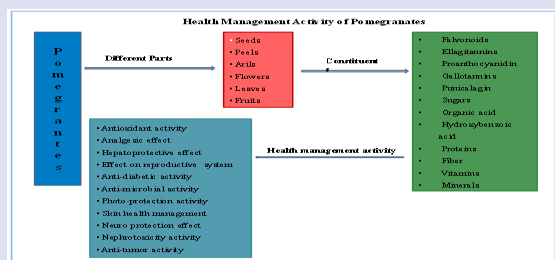
REFERENCES

- Rahmani, AH, Shabrmi FMA, Allemailem KS, Aly SM, Khan MA. Implications of green tea and its constituents in the prevention of cancer via the modulation of cell signalling pathway. *Biomed Res Int.* 2015;9:25640.
- Rahmani AH, Aly SM, Ali H, Babiker AY, Srikar S, Khan AA. Therapeutic effects of date fruits (*Phoenix dactylifera*) in the prevention of diseases via modulation of anti-inflammatory, anti-oxidant and anti-tumour activity. *Int J Clin Exp Med.* 2014;7(3):483-91.
- Li Y, Guo C, Yang J, Wei J, Xu J, Cheng S. Evaluation of antioxidant properties of pomegranate peel extract in comparison with pomegranate pulp extract. *Food Chem.* 2006;96(2):254-60.
- Vroegrijk IOCM, van Diepen JAS, Van den Berg *et al.* Pomegranate seed oil, a rich source of punicic acid, prevents diet-induced obesity and insulin resistance in mice. *Food and Chemical Toxicology.* 2011;49(6):1426-30.
- Seeram N, Lee R, Hardy M, Heber D. Rapid large scale purification of ellagitanins from pomegranate husk, a by-product of the commercial juice industry. *Separation and Purification Technology.* 2005;41(1):49-55.
- Noda Y, Kaneyuki T, Mori A, Packer L. Antioxidant activities of pomegranate fruit extract and its anthocyanidins: delphinidin, cyanidin, and pelargonidin. *J Agric Food Chem.* 2002;50(1):166-71.
- Shukla M, Gupta K, Rasheed Z, Khan KA, Haqqi TM. Consumption of hydrolyzable tannins-rich pomegranate extract suppresses inflammation and joint damage in rheumatoid arthritis. *Nutrition.* 2008;24(7):733-43.
- Mirdehghan SH, Rahemi M. Seasonal changes of mineral nutrients and phenolics in pomegranate (*Punica granatum* L.) fruit. *Sci Hort.* 2007;111(2):120-7.
- Jaiswal V, DerMarderosian A, Porter JR. Anthocyanins and polyphenol oxidase from dried arils of pomegranate (*Punica granatum* L.). *Food Chemistry.* 2010; 118(1):11-6.

10. Gil MI, Tomás-Barberán FA, Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *Journal of Agricultural and Food chemistry*. 2000;48(10):4581-9.
11. Van Elswijk DA, Schobel UP, Lansky EP, Irth H, van der Greef J. Rapid dereplication of estrogenic compounds in pomegranate (*Punica granatum*) using on-line biochemical detection coupled to mass spectrometry. *Phytochemistry*. 2004;65(2):233-41.
12. Seeram NP, Aviram M, Zhang Y, Henning SM, Feng L, *et al.* Comparison of antioxidant potency of commonly consumed polyphenol-rich beverages in the United States. *Journal of agricultural and food chemistry*. 2008;56(4):1415-22.
13. Fischer UA, Carle R, Kammerer DR. Identification and quantification of phenolic compounds from pomegranate (*Punica granatum* L.) peel, mesocarp, aril and differently produced juices by HPLC-DAD-ESI/MS n. *Food chemistry*. 2011;127(2):807-21.
14. Mena P, García-Viguera C, Navarro-Rico J, Moreno DA, Bartul J, *et al.* Phytochemical characterisation for industrial use of pomegranate (*Punica granatum* L.) cultivars grown in Spain. *Journal of the Science of Food and Agriculture*. 2011;91(10):1893-906.
15. Qu W, Breksa III AP, Pan Z, Ma H. Quantitative determination of major polyphenol constituents in pomegranate products. *Food Chemistry*. 2012;132(3):1585-91.
16. Fischer UA, Dettmann JS, Carle R, Kammerer DR. Impact of processing and storage on the phenolic profiles and contents of pomegranate (*Punica granatum* L.) juices. *European Food Research and Technology*. 2011;233(5):797-816.
17. Melgarejo P, Salazar DM, Artes F. Organic acids and sugars composition of harvested pomegranate fruits. *European Food Research and Technology*. 2000;211(3):185-90.
18. Tezcan F, Gültekin-Özgülven M, Diken T, Özçelik B, Erim FB. Antioxidant activity and total phenolic, organic acid and sugar content in commercial pomegranate juices. *Food Chemistry*. 2009;115(3):873-7.
19. Amakura Y, Okada M, Tsuji S, Tonogai Y. High-performance liquid chromatographic determination with photodiode array detection of ellagic acid in fresh and processed fruits. *Journal of Chromatography A*. 2000;896(1):87-93.
20. Singh RP, Gupta AK, Bhatia AK. Utilization of wild pomegranate in North West Himalayas-Status and Problems. In: *Proceedings of National Seminar on Production and Marketing of Indigenous Fruits*, New Delhi 1990 (pp. 100-107).
21. Singh, D. Sethi, V. Screening of pomegranate genotypes for the preparation of quality grade anardana. *Journal of food science and technology*. 2003;40(2):236-8.
22. El-Nemr SE, Ismail IA, Ragab M. Chemical composition of juice and seeds of pomegranate fruit. *Molecular Nutrition & Food Research*. 1990;34(7):601-6.
23. Syed, D.N., Afaq, F. & Mukhtar, H. Pomegranate Derived Products for Cancer Chemoprevention. *Seminars in Cancer Biology*, 2007;17:377-385
24. Rahmani AH. Cassia fistula Linn: Potential candidate in the health management. *Pharmacognosy research*. 2015;7(3):217.
25. Rahmani AH, Albutti AS, Aly SM. Therapeutics role of olive fruits/oil in the prevention of diseases via modulation of anti-oxidant, anti-tumour and genetic activity. *International journal of clinical and experimental medicine*. 2014; 7(4):799-808.
26. Rahmani AH, Aldebasi YH. Potential role of carica papaya and their active constituents in the prevention and treatment of diseases. *Int J Pharm Pharm Sci*. 2016;8:11-15
27. Singh RP, Chidambara Murthy KN, Jayaprakasha GK. Studies on the antioxidant activity of pomegranate (*Punica granatum*) peel and seed extracts using *in vitro* models. *Journal of agricultural and food chemistry*. 2002;50(1):81-6.
28. Kotamballi N, Chidambara Murthy, [†] Guddadarangavvahally K, Jayaprakasha, Ravendra P. Singh. Studies on Antioxidant Activity of Pomegranate (*Punica granatum*) Peel Extract Using *in vivo* Models. *J. Agric. Food Chem*. 2002; 50(17):4791-95.
29. Ashoush IS, El-Batawy OI, El-Shourbagy GA. Antioxidant activity and hepatoprotective effect of pomegranate peel and whey powders in rats. *Annals of Agricultural Sciences*. 2013;58(1):27-32.
30. Zhang LH, Li LL, Li YX, Zhang YH. *In vitro* antioxidant activities of fruits and leaves of pomegranate. *Acta Hort*, 2008;765:31-4.
31. Sadeghi N, Jannat B, Oveisi MR, Hajimahmoodi M, Photovat M. Antioxidant activity of Iranian pomegranate (*Punica granatum* L.) seed extracts. *Journal of Agricultural Science and Technology*. 2010;11:633-8.
32. Bagri P, Ali M, Aeri V, Sultana S, Bhowmik M. Evaluation of anti-inflammatory and analgesic activity of *Punica granatum* linn. *Int J Drug Dev Res*. 2010;2:698-702
33. Mo J, Panichayupakaranant P, Kaewnopparat N, Nitruangjaras A, Reanmongkol W. Topical anti-inflammatory and analgesic activities of standardized pomegranate rind extract in comparison with its marker compound ellagic acid *in vivo*. *Journal of ethno pharmacology*. 2013;148(3):901-8.
34. González-Trujano ME, Pellicer F, Mena P, Moreno DA, García-Viguera C. Antinociceptive and anti-inflammatory activities of a pomegranate (*Punica granatum* L.) extract rich in ellagitannins. *International journal of food sciences and nutrition*. 2015;66(4):395-9.
35. Labib RM, El-Ahmady SH. Antinociceptive, anti-gastric ulcerogenic and anti-inflammatory activities of standardized egyptian pomegranate peel extract. *Journal of Applied Pharmaceutical Science*. 2015;5:048-051.
36. Mo J, Panichayupakaranant P, Kaewnopparat N, Nitruangjaras A, Reanmongkol W. Wound healing activities of standardized pomegranate rind extract and its major antioxidant ellagic acid in rat dermal wounds. *Journal of natural medicines*. 2014;68(2):377-86.
37. Larrosa M, González-Sarriás A, Yáñez-Gascón MJ, Selma MV, Azorín-Ortuño M, Toti S, Tomás-Barberán F, Dolara P, Espín JC. Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on phenolic metabolism. *The Journal of nutritional biochemistry*. 2010;21(8):717-25.
38. Ahmed S, Wang N, Hafeez BB, Cheruvu VK, Haqqi TM. *Punica granatum* L. extract inhibits IL-1 β -Induced expression of matrix metalloproteinase by inhibiting the activation of MAP kinases and NF- κ B in human chondrocytes *in vitro*. *The Journal of nutrition*. 2005;135(9):2096-102.
39. Singh RP, Chidambara Murthy KN, Jayaprakasha GK. Studies on the antioxidant activity of pomegranate (*Punica granatum*) peel and seed extracts using *in vitro* models. *Journal of agricultural and food chemistry*. 2002;50(1):81-6.
40. Toklu HZ, Sehirli O, Sener G, Dumlu MU, Ercan F, *et al.* Pomegranate peel extract prevents liver fibrosis in biliary-obstructed rats. *Journal of Pharmacy and Pharmacology*. 2007;59(9):1287-95.
41. Al-Olayan EM, El-Khadragy MF, Metwally DM, Moneim AE. Protective effects of pomegranate (*Punica granatum*) juice on testes against carbon tetrachloride intoxication in rats. *BMC complementary and alternative medicine*. 2014; 14(1):164.
42. Leiva KP, Rubio J, Peralta F, Gonzales GF. Effect of *Punica granatum* (pomegranate) on sperm production in male rats treated with lead acetate. *Toxicology Mechanisms and Methods*. 2011;21(6):495-502.
43. Türk G, Sönmez M, Aydın M, Yüce A, Gür S, *et al.* Effects of pomegranate juice consumption on sperm quality, spermatogenic cell density, antioxidant activity and testosterone level in male rats. *Clinical nutrition*. 2008;27(2):289-96.
44. Azadzoi KM, Schulman RN, Aviram M, Siroky MB. Oxidative stress in arteriogenic erectile dysfunction: prophylactic role of antioxidants. *The Journal of urology*. 2005;174(1):386-93.
45. Das S, Barman S. Antidiabetic and antihyperlipidemic effects of ethanolic extract of leaves of *Punica granatum* in alloxan-induced non-insulin-dependent diabetes mellitus albino rats. *Indian journal of pharmacology*. 2012;44(2):219.
46. Kartik J, Salwe, Devender O, Sachdev, Yogesh Bahurupi, and Manimekalai Kumarappan. Evaluation of antidiabetic, hypolipidemic and antioxidant activity of hydroalcoholic extract of leaves and fruit peel of *Punica granatum* in male Wistar albino rats. *J Nat Sci Biol Med*. 2015;6:56-62.
47. Radhika S, Smila KH, dan Mutezhilhan R. Antidiabetic and Hypolipidemic Activity of *Punica granatum* Linn on Alloxan Induced Rats. *World Journal of Medical Sciences*. 2011; 6: 178-82.
48. Das S, Sama G. Antidiabetic Action of Ethanolic Extracts of *Punica granatum* Linn. in Alloxan-induced Diabetic Albino Rats. *Stamford Journal of Pharmaceutical Sciences*. 2009;2(1):14-21.
49. Dahanukar SA, Kulkarni RA, Rege NN. Pharmacology of medicinal plants and natural products. *Indian journal of pharmacology*. 2000;32(4):S81-118.
50. Cowan MM. Plant products as antimicrobial agents. *Clinical microbiology reviews*. 1999;12(4):564-82.
51. Devatkal SK, Jaiswal P, Jha SN, Bharadwaj R, Viswas KN. Antibacterial activity of aqueous extract of pomegranate peel against *Pseudomonas stutzeri* isolated from poultry meat. *Journal of food science and technology*. 2013;50(3):555-60.
52. Al-Zoreky NS. Antimicrobial activity of pomegranate (*Punica granatum* L.) fruit peels. *International journal of food microbiology*. 2009;134(3):244-8.
53. Nuamsetti T, Dechayuenyong P, Tantipabulvut S. Antibacterial activity of pomegranate fruit peels and arils. *Science Asia*. 2012;38(3):319-22.
54. Sadeghian A, Ghorbani A, Mohamadi-Nejad A, Rakhshandeh H. Antimicrobial activity of aqueous and methanolic extracts of pomegranate fruit skin. *Avicenna J Phytomed*. 2011;1:67-73.
55. Zhang J, Zhan B, Yao X, Gao Y, Song J. Antiviral activity of tannin from the pericarp of *Punica granatum* L. against genital Herpes virus *in vitro*. *China journal of Chinese materia medica*. 1995;20(9):556-8.
56. Sundararajan A, Ganapathy R, Huan L, Dunlap JR, Webby RJ, *et al.* Influenza virus variation in susceptibility to inactivation by pomegranate polyphenols is determined by envelope glycoproteins. *Antiviral research*. 2010;88(1):1-9.
57. Dahham SS, Ali MN, Tabassum H, Khan M. Studies on antibacterial and antifungal activity of pomegranate (*Punica granatum* L.). *Am. Eurasian J. Agric. Environ. Sci*. 2010;9(3):273-81.
58. Anibal PC, Peixoto IT, Foglio MA, Höfling JF. Antifungal activity of the ethanolic extracts of *Punica granatum* L. and evaluation of the morphological and structural modifications of its compounds upon the cells of *Candida* spp. *Brazilian Journal of Microbiology*. 2013;44(3):839-48.
59. Reddy MK, Gupta SK, Jacob MR, Khan SI, Ferreira D. Antioxidant, antimalarial and antimicrobial activities of tannin-rich fractions, ellagitannins and phenolic acids from *Punica granatum* L. *Planta medica*. 2007;53(05):461-7.
60. Mubarak MA, Hafiz TA, Dkhil MA, Al-Quraishy S. Beneficial effect of *Punica granatum* peel extract on murine malaria-induced spleen injury. *BMC Complementary and Alternative Medicine*. 2016;16(1):221.

61. Dell'Agli M, Galli GV, Bulgari M, Basilio N, Romeo S, *et al.* Ellagitannins of the fruit rind of pomegranate (*Punica granatum*) antagonize *in vitro* the host inflammatory response mechanisms involved in the onset of malaria. *Malaria Journal*. 2010;9(1):208.
62. Qnais EY, Elokda AS, Abu Ghalyun YY, Abdulla FA. Antidiarrheal Activity of the Aqueous Extract of *Punica granatum* (Pomegranate) Peels. *Pharmaceutical Biology*. 2007;45(9):715-20.
63. Ichihashi M, Ando H, Yoshida M, Niki Y, Matsui M. Photoaging of the skin. *Anti-Aging Medicine*. 2009;6(6):46-59.
64. Aslam MN, Lansky EP, Varani J. Pomegranate as a cosmeceutical source: pomegranate fractions promote proliferation and procollagen synthesis and inhibit matrix metalloproteinase-1 production in human skin cells. *Journal of ethnopharmacology*. 2006;103(3):311-8.
65. Pacheco-Palencia LA, Noratto G, Hingorani L, Talcott ST, Mertens-Talcott SU. Protective effects of standardized pomegranate (*Punica granatum* L.) polyphenolic extract in ultraviolet-irradiated human skin fibroblasts. *Journal of agricultural and food chemistry*. 2008;56(18):8434-41.
66. Afaq F, Zaid MA, Khan N, Dreher M, Mukhtar H. Protective effect of pomegranate-derived products on UVB-mediated damage in human reconstituted skin. *Experimental dermatology*. 2009;18(6):553-61.
67. Lei F, Zhang XN, Wang W, Xing DM, Xie WD, *et al.* Evidence of anti-obesity effects of the pomegranate leaf extract in high-fat diet induced obese mice. *International Journal of Obesity*. 2007;31(6):1023-9.
68. Kote S, Kote S, Nagesh L. Effect of pomegranate juice on dental plaque microorganisms (streptococci and lactobacilli). *Ancient science of life*. 2011;31(2):49-52.
69. Menezes SM, Cordeiro LN, Viana GS. *Punica granatum* (pomegranate) extract is active against dental plaque. *Journal of herbal pharmacotherapy*. 2006;6(2):79-92.
70. DiSilvestro RA, DiSilvestro DJ, DiSilvestro DJ. Pomegranate extract mouth rinsing effects on saliva measures relevant to gingivitis risk. *Phytotherapy Research*. 2009;23(8):1123-7.
71. Viuda-Martos M, Fernández-López J, Pérez-Álvarez JA. Pomegranate and its many functional components as related to human health: a review. *Comprehensive Reviews in Food Science and Food Safety*. 2010;9(6):635-54.
72. Mohan M, Waghulde H, Kasture S. Effect of pomegranate juice on Angiotensin II-induced hypertension in diabetic wistar rats. *Phytotherapy Research*. 2010;24(S2):S196-203.
73. Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, *et al.* Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *The American journal of clinical nutrition*. 2000;71(5):1062-76.
74. de Nigris F, Williams-Ignarro S, Botti C, Sica V, Ignarro LJ, Napoli C. Pomegranate juice reduces oxidized low-density lipoprotein downregulation of endothelial nitric oxide synthase in human coronary endothelial cells. *Nitric Oxide*. 2006;15(3):259-63.
75. Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis*. 2001;158(1):195-8.
76. Aviram M, Rosenblat M, Gaitini D, Nitecki S, Hoffman A, *et al.* Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clinical Nutrition*. 2004;23(3):423-33.
77. Braidy N, Selvaraju S, Essa MM, *et al.* Neuroprotective effects of a variety of pomegranate juice extracts against MPTP-induced cytotoxicity and oxidative stress in human primary neurons. *Oxidative medicine and cellular longevity* 2013.
78. Subash S, Essa MM, Al-Asmi A, Al-Adawi S, Vaishnav R, *et al.* Pomegranate from Oman alleviates the brain oxidative damage in transgenic mouse model of Alzheimer's disease. *Journal of traditional and complementary medicine*. 2014;4(4):232-8.
79. Dolatshahi M, Farbood Y, Sarkaki A, Mansouri SM, Khodadadi A. Ellagic acid improves hyperalgesia and cognitive deficiency in 6-hydroxydopamine induced rat model of Parkinson's disease. *Iranian journal of basic medical sciences*. 2015 Jan;18(1):38-46.
80. El-Habibi EM. Renoprotective effects of *Punica granatum* (pomegranate) against adenine-induced chronic renal failure in male rats. *Life Sci J*. 2013;10(4):2059-69.
81. El-Daly AA. Pomegranate peels Extract Protects Cadmium-induced nephrotoxicity in albino mice. *Journal of Bioscience and Applied Research*. 2016;2: 362-75.
82. Sadeghi F, Nematbakhsh M, Noori-Diziche A, Eshraghi-Jazi F, Talebi A, *et al.* Protective effect of pomegranate flower extract against gentamicin-induced renal toxicity in male rats. *Journal of renal injury prevention*. 2015;4(2):45.
83. Dai Z, Nair V, Khan M, Ciolino HP. Pomegranate extract inhibits the proliferation and viability of MMTV-Wnt-1 mouse mammary cancer stem cells *in vitro*. *Oncology reports*. 2010;24(4):1087.
84. Dai Z, Nair V, Khan M, Ciolino HP. Pomegranate extract inhibits the proliferation and viability of MMTV-Wnt-1 mouse mammary cancer stem cells *in vitro*. *Oncology reports*. 2010;24(4):1087.
85. Dikmen M, Ozturk N, Ozturk Y. The antioxidant potency of *Punica granatum* L. Fruit peel reduces cell proliferation and induces apoptosis on breast cancer. *Journal of Medicinal Food*. 2011;14(12):1638-46.

GRAPHICAL ABSTRACT



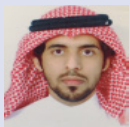
HIGHLIGHTS OF PAPER

- Pomegranates fruits have innumerable health benefits and its implication in diseases cure.
- Fruits, seeds, peel and leaves of pomegranate contain numerous valuable ingredients and such ingredients show therapeutic implications in the health management.
- Pomegranate has proven anti-inflammatory role through the modulation of enzymes linked with inflammatory process.
- *Punica granatum* has established effective role in the inhibition of microorganism growth.

AUTHOR PROFILE



Arshad Husain Rahmani: Is working as an Assistant Professor in the Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University, Kingdom of Saudi Arabia. His research interests include measurement of the therapeutic potential of natural compounds in the management of diseases and expression pattern of the genes linked to cancer development and progression. Currently he is working on research projects funded by Research Scientific Deanship, Qassim University and National Science Technology Innovation Program of Ministry of Education (NSTIP), Saudi Arabia. He has published more than 35 research and review article, of international repute. Besides this, he is an active reviewer of several ISI indexed journals.



Saleh A. Almatroodi: Is a researcher and an assistant professor in laboratory medicine at Qassim University. He is the chairman of Radiologic Technology Department and the head of E-learning unit in college of applied medical sciences. He has published several meaningful research papers in international repute journal and has presented his papers in many national and international conferences



Mohammed A. Alsahli: Is an Assistant Professor in Medical Laboratory Sciences at Qassim University. His research interests involve medical laboratory sciences in general, particularly oncology, platelet biology and haemostatic regulation in prothrombotic diseases. Mohammed is currently the chairman of Medical Laboratories Department, College of Applied Medical Sciences, Qassim University, Saudi Arabia.

Cite this article : Rahmani AH, Alsahli MA, Almatroodi SA. Active Constituents of Pomegranates (*Punica granatum*) as Potential Candidates in the Management of Health through Modulation of Biological Activities. *Pharmacog J*. 2017;9(5):689-95.