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PHYTOCHEMICAL SCREENING AND EVALUATION OF ANTI EMETIC ACTIVITY OF *PUNICA GRANATUM* LEAVES

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ABSTRACT

The pomegranate, *Punica granatum* belongs to family Lythraceae is an ancient, mystical, unique fruit borne on a small long-living tree cultivated throughout the mediterranean region, as far north as the Himalayas, in Southeast Asia, and in California and Arizona in the United States. *Punica granatum* is a fruit bearing deciduous herb or small tree growing between 5-8m tall. *Punica granatum* leaves are used as bitter tonic in fever and used in pneumonia, flu, mouth and lip infections. In recent studies plant has shown anti fungal, immunosuppressant and anti diabetic activity. It is also used in treatment of heart problems, stomach disorders, dental care, cancer, anaemia, osteoarthritis. *Punica* including *Punica protopunica* are known to exhibit strong anti oxidant activity. The presence of phytoconstituents like alkaloids and terpenoids in the extract might be responsible for the anti emetic activity. However, the anti emetic property of ethanol extract of *Punica granatum* leaves have not been carried out till today. Hence, in present investigation, the extract of *Punica granatum* dried leaves was screened for preliminary phytochemical composition and anti emetic activity by using standard procedures. The results illustrated that the extract of the leaves have anti emetic potential comparable with that of metoclorpramide (reference drug).

KEY-WORDS: *Punica granatum,* anti emetic, metaclopramide, flavonoids.

INTRODUCTION

For centuries, medicinal herbs have been used to treat all types of health maladies. In fact, modern medicine is essentially based on herbal medicine. Even today in the times of advanced technology and medical science still depend on plants for their healing. These me-dicinal plants consider as a rich source of ingredients which can be used in drug develop-ment and synthesis. Medicinal plants exhibit phytotherapeutic effects caused by biologically active compounds specific secondary metabolites. The plants have been utilized for basic and curative health care since time immemorial. The use of plants as food and medicines started ever since man started life on the planet. The plant kingdom is a virtual goldmine of potential drug targets and other active drug molecules waiting to be discovered. During the last decade, use of traditional medicine has expanded globally and gained popularity. Plant based drugs are having a revived interest now-a-days because of awareness of deleterious effects of modern synthetic drugs. Natural products can play a very crucial role in pharmaceutical industry as drug them or as drug carrier or bio-enhancers or excipients. The importance of herbal/plant medicines is well documented in Vedas, which proved to be the ancient literature. The properties of the plants and their remedies are given in detail and in fact Ayurveda is the very principle root for the emergence of Ancient medical science in India that gave origin to branches like Sushruta and Charka Samhita. In order to set up quality in production and products, research documentation is mandatory to supply to international requirements. By referring global standards and international pharmacopoeia like Herbal B.P, China, Japanese Herbal, Ayurvedic Formulary of India, WHO Guidelines on Herbal Medicines, this could be met with. If the Indian herbal industry, is to survive in the domestic and international markets steps have to be taken to establish a good quality control mechanism, for which the government should consider assisting the standardization of drugs to meet International requirements in the coming years. It is also necessary to integrate modern knowledge with traditional knowledge. The drugs and products of the industry are working on the scientifically defined techniques and explained with modern biological and chemical definitions and tools, and that alone will give a therapeutically active herbal original drug available for health care worldwide.

Punica granatum L. has been widely used by traditional medicine in America, Asia, Africa and Europe for the treatment of different types of diseases. Many Indian medicinal plants recommended for the treatment of diabetes mellitus lack rigorous scientific justification. *Punica granatum*, commonly known as

pomegranate is one of the plants that have long been used in traditional herbal medicine against differ diseases. A symbol of fecundity and divine femininity emerges, whose fruit rinds, bark and roots are used worldwide as taenicides, owing to alkaloids, and treatment of diarrhea and oral and genital lesions, owing to tannins and astringency. The seeds contain oil which contains not only the steroidal estrogen, estrone, in the highest concentration found in any botanical species, but also a full range of non-steroidal phytoestrogens including the comesten, coumestrol, and the isoflavones, genistein and daidzein. Both the juice and the oil contain numerous and diverse bioflavonoid, which have been shown to be both potently antioxidant and inhibitory of one or both of the enzymes cyclooxygenase (catalyzing arachidonic acid to prostaglandins) and lipoxygenase (catalyzing arachidonic acid to leukotrienes). Extracts of the rinds have been shown to be bactericidal, antiviral, antitumor and use of pomegranates in the treatment of Acquired Immune Deficiency Syndrome (AIDS) owing to their antioxidant properties and botanical uniqueness.

An anti emetic is a drug that is effective against vomiting and nausea. These are typically used to treat motion sickness and side effects of opiod analgesics, general anaesthetics, and chemotherapy directed against cancer. The development of effective anti emetic prophylaxis is one of the most significant steps forward in the area of supportive care. *Punica granatum* leaves are one of the efficient crude drugs which have anti emetic activity. Punica granatum is native to a region from Iran to Northern India. The *Punica granatum* leaves have been used in natural and holistic medicine to treat sore throat, cough, urinary infections, digestive disorders, arthritis etc. clinical research shows that pomegranates when part of healthy diet might help prevent heart diseases, heart attacks and strokes. Over the past decade, significant progress has been made in establishing the pharmacological mechanisms of *Punica granatum* leaves and the individual consituents responsible for them. The current research seems to indicate the most therapeutically beneficial *Punica granatum* leaves constituents are ellagic acid, ellagitammins, punicic acid, flavonoids, anthocyanidins, anthocyanins and estrogenic flavonols and flavones.

Plant profile

Botanical name- *Punica granatum*
Kingdom: Plantae (Angiosperms)
Order: Myrtales
Family: Lythraceae
Genus: Punica
Species: *P. Granatum*
The pomegranate has glossy, leathery leaves that are narrow and lance-shaped.

Fig. No. 1: *Punica granatum* plant

Fig. No. 2: *Punica granatum* leaves

MATERIALS AND METHODS

Plant Material: The plant material was collected from Boduppal, Ranga Reddy dist, Telagana, India. It was identified by Dr. B. Prathibha Devi, Department of Botany, Osmania University, Hyderabad. Voucher no. 0668 of the plant was deposited in the Department of Botany, Osmania University, Hyderabad. The plant material was air-dried under the shade at room temperature. Dried plant material was pulverized and the powder kept in polyethylene bags for future expiremental pupose.

Experimental Animals: 2-4 days old male chicks (32-52gm) were obtained from poultry. After 24 hrs fasting, the antiemetic activity was evaluated. All chicks were kept under laboratory conditions at room temperature with 12hr light and dark cycles. The experimental protocol was duly approved by institutional animal ethics committee (IAEC) and care of the animals was carried out as per the guidelines of committee for the purpose of control and supervision of experiments on animals.

(CPCSEA) (IAEC:1/IAEC/LCP/0109/2015/ck80).

Drugs, Chemicals, Reagents: Metaclopramide hydrochloride was purchased from IPCA Laboratories, Hyderabad. Copper sulphate, Tween 80, Acetic anhydride, Sulphuric acid, Lead acetate, Nitric acid, Copper acetate and all other reagents were purchased from SD Fine Chemicals Limited.

Preparation of Extracts: Accurately weighed plant material (dried leaves) was extracted with ethanol by using Soxhlet apparatus. Solvent recovery was done by using simple distillation method. Extract was collected and stored in refrigerator.

Preliminary Phytochemical Screening: The different chemical tests were performed for establishing profile of the leaves extract for its chemical composition; the following chemical tests for various phytoconstituents in the ethanol extract was carried out as described below.

(A) Test for alkaloids

i) Dragendroff's Test: In a test tube containing 1ml of extract, few drops of Dragendroff's reagent was added and the color developed was noticed. Appearance of orange color indicates the presence of alkaloids.

ii) Wagner's Test: To the extract, 2 ml of Wagner's reagent was added; the formation of a reddish brown precipitate indicates the presence of alkaloids.

ii) Mayer's Test: To the extract, 2 ml of Mayer's reagent was added, a dull white precipitate revealed the presence of alkaloids.

iv) Hager's Test: To the extract, 2 ml of Hager's reagent was added; the formation of yellow precipitate confirmed the presence of alkaloids.

(B) Test for terpenoids

i) Salkowski test: To 1 ml of extract, tin (one bit) and thionyl chloride were added. Appearance of pink color indicates the presence of terpenoids.

ii) Hirshonn reaction: When the substance was heated with trichloroacetic acid, red to purple colour was observed.

(C) Test for steroids

i) Liebermann Burchard Test: To 1ml of extract, 1ml of glacial acetic acid and 1ml of acetic anhydride and two drops of concentrated sulphuric acid were added. The solution become red, then blue and finally bluish green indicates the presence of steroids.

(D) Test for coumarins

To 1 ml of extract, 1 ml of 10% sodium hydroxide was added. The presence of coumarins is indicated by the formation of yellow color.

(E) Test for tannins

i) To few mg of extract, ferric chloride was added, formation of a dark blue or greenish black color showed the presence of tannins.

ii) The extract was mixed with basic lead acetate solution; formation of white precipitate indicated the presence of tannins.

(F) Test for saponins: To 1 ml of the extract, 5 ml of water was added and the tube was shaken vigorously. Copious lather formation indicates the presence of saponins.

(G) Test for flavones

i) Shinoda Test: To the extract, a few magnesium turnings and 2 drops of concentrated hydrochloric acid were added, formation of red color showed the presence of flavones.

ii) To the extract, 10% sodium hydroxide or ammonia was added; dark yellow color shows the presence of flavones.

(H) Test for quinones: To 1 ml of the extract 1 ml of concentrated sulphuric acid was added. Formation of red color shows the presence of quinones.

(I) Test for flavanones

i) To the extract, 10% sodium hydroxide was added and the colour changes from yellow to orange, which indicates the presence of flavanones.

ii) To the extract, conc. sulphuric acid was added, and the colour changes from orange to crimson red, which indicates the presence of flavanones.

(J) Test for anthocyanins
i) To the extract, 10% sodium hydroxide was added, and the blue color shows the presence of anthocyanins.
ii) To the extract, conc. sulphuric acid was added, and the yellowish orange color confirms the presence of anthocyanins.

(K) Test for anthraquinones
Borntrager's test: The extract was macerated with ether and after filtration, aqueous ammonia or caustic soda was added. Pink red or violet color in the aqueous layer after shaking indicates the presence of anthraquinones.

(L) Test for phenols
Ferric chloride test: To the extract, few drops of 10 % aqueous ferric chloride were added. Appearance of blue or green color indicates the presence of phenols.

(M) Test for proteins
i) Biuret Test: To the extract, 1 ml of 40% sodium hydroxide solution and two drops of one percent copper sulphate solution were added. Formation of violet color indicates the presence of proteins.

ii) Xanthoprotein Test: To the extract, 1 ml of concentrated nitric acid was added. A white precipitate was formed, it is then boiled and cooled. Then, 20% sodium hydroxide or ammonia was added. Orange color indicates the presence of aromatic amino acids.

iii) Tannic Acid Test: To the extract, 10% tannic acid was added. Formation of white precipitate indicates the presence of proteins.

(N) Test for carbohydrates
i) Molisch's Test: To the extract, 1 ml of alpha-naphthol solution, and concentrated sulphuric acid through the sides of test tube were added. Purple or reddish violet color at the junction of the two liquids revealed the presence of carbohydrates.

ii) Fehling's Test: To the extract, equal quantities of fehling's solution A and B were added and on heating, formation of a brick red precipitate indicates the presence of carbohydrates.

iii) Benedict's Test: To 5 ml of Benedict's reagent, extract was added and boiled for two minutes and cooled. Formation of red precipitate showed the presence of carbohydrates.

(O) Test for amino acids
Ninhydrin test: Two drops of ninhydrin solution were added to the extract, a characteristic purple color indicates the presence of amino acids.

(P) Test for Fixed Oils and Fats
i) Spot Test: A small quantity of extract was pressed between two filter papers. Oil stains on the paper indicates the presence of fixed oils and fats.

Anti-Emetic Activity: Anti-Emetic effect was determined by calculating the mean decreases in number of retching following the protocols, Akita et .al, 1992. Chicks are divided into three groups of five chicks each. Chicks were kept in beaker at 25^0C for 10 min. The ethanolic extract of *Punica granatum* was dissolved in 1% Tween 80 and administered at a dose of 50mg/kg, 100mg/kg, 200mg/kg orally and volume of 10 ml/kg to test animal on the basis of body weight. Control group received only 1% Tween 80. Metoclopramide was used as standard drug (50 mg/kg) body weight intra peritoneally. 10 min. later 50 mg anhydrous copper sulphate /kg body weight was administered orally to each chick, then the number of retches (an emetic action without vomiting gastric material) was counted for next 10 min. The Anti-Emetic Effect was assessed as the decreasing the number of retches in the treated group in contrast to the control. The inhibition 95% was calculated as below

Inhibition (%) = {(A-B)/A}*100
Where, A is the control frequency of retches
B is the frequency of retching the treated group.

RESULTS AND DISCUSSION

Preliminary Phytochemical Screening: In the preliminary phytochemical screening was found that the ethanolic dried leaves extract contain alkaloids, phytosterols, diterpenes, saponins.

Table no: 1 Preliminary phytochemical screening of *Punica granatum* leaves

Constituents	Ethanol extract
Terpenoids	+
Saponins	+
Steroids	+
Carbohyrates	-
Flavonoids	+
Alkaloids	+
Quinones	-
Tannins	-
Fixed oils and fats	-
Phenols	-
Glycosides	-

Amino acids	-
Anthraquinones	-

(+) Present, (-) Absent

Anti-Emetic Activity: Result of the antiemetic activity of ethanol extract of *Punica granatum* leaves was given in Table 2. After administration of a dose of 50mg/kg body weight metoclopramide and the extract of leaves (50 mg/kg, 100 mg/kg, 200 mg/kg body weight respectively), the number of retches were reduced. The group of chicks treated with metoclopramide was found to have 15.8 ± 1.428 retches as compared to the 68.6 ± 2.482 retches of control group, thus metoclopramide reduced the retches by 76.968%. The chicks treated with root extract 50 mg/kg inhibited the retches up to 22.741%, 100 mg/kg inhibited the retches up to 48.688% and 200 mg/kg inhibited the retches up to 73.761%. Therefore, ethanol extract of 200 mg/kg inhibited emesis to an extent equal to metoclopramide at 50mg/kg.

Table 2: Antiemetic activity of ethanol extract of *Punica granatum* leaves

S. No.	Drug / Dose	Number of retches (Mean ± S. E. M)	% Inhibition
1	Control (10ml/kg)	68.6 ± 2.482	-
2	Metoclopramide	15.8 ± 1.428	76.968
3	Extract (50 mg/kg)	51± 1.755	22.741
4	Extract (100 mg/kg)	33.2 ± 1.594	48.688
5	Extract (200 mg/kg)	16 ± 1.225	73.761

S.E.M= Standard Error Mean

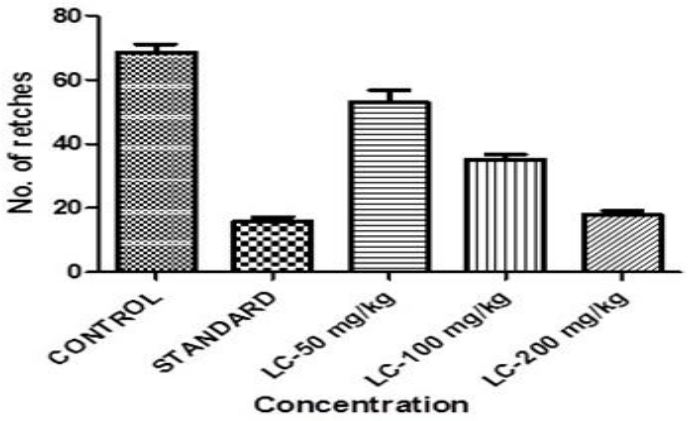

Fig. no. 3: Number retches for control, standard and ethanolic extract of *Punica granatum* leaves at different doses

The results illustrated that the extracts of leaf have anti emetic potential comparable with that of metoclopramide (the reference drug). Retching may occur after administration of cancer chemotherapeutic agents. Chemotherapy induced nausea and vomiting (CINV) is a common side effect of many cancer treatments. Chemotherapeutic agents or their metabolites can directly activate the medullary chemo receptor trigger zone or vomiting centre or act peripherally by causing cell damage in the gastrointestinal tract and releasing serotonin from entero chromaffin cells of the small intestinal mucosa. The released serotonin activates 5-HT receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response (Hosseinzadeh. H, 2008; Sontakke, .V, 2003; Bulbul. L, 2013). It has also been established that the peripheral 5-HT receptors play an important role in copper sulphate induced emesis.

Although the results are significant but the mode of action is not known. *Punica granatum* leaves reduces copper sulphate induced retching in young chicks, possibly by peripheral action as the oral copper sulphate induces emesis by peripheral action through excitation of visceral afferent nerve fibers of the gastro intestinal tract (Hosseinzadeh. H., 2008; zia-ui-haq.M., 2012). This study also justifies the traditional use of *punica granatum* in GIT complaints. From chemical point of view, leaf of *punica granatum* containing alkaloids and terpenes showed significant activity as compared to standard. Therefore it may be said that alkaloidal contents may play some role in antiemetic effect (HasanMMU, 2012). Further studies are required to determine the exact mode of action and the active compounds responsible for these effects.

CONCLUSION

The development of effective antiemetic prophylaxis is one of the most significant steps forward in the area of

supportive care. This development has not only led to improve efficacy but also to a decrease risk associated with the use of Antiemetics. The results of this study suggest that the ethanol extracts of *punica granatum* (200 mg/kg) have protective effect against copper sulphate induced–retching in young chickens, possibly by peripheral and central mechanisms. The potential of this extract as antiemetic activity may be due to the presence of phytoconstituents like alkaloids and terpenes and might be responsible for its activity. Further studies (including the analysis and identification of the specific active compounds, toxicological and haematological studies) with this plant extract should be carried out using higher animal models, in order to authenticate it as a potent antiemetic agent. These local ethno medical preparations of plant sources should be scientifically evaluated and then disseminated properly. This knowledge about the medicinal plants usage can also be extended to other fields like field of pharmacology.

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