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# Pomegranate Tincture (*Punica granatum L.*) Showing Antiangiogenic Activity on Chicken Egg embryo CAM Assay

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**Abstract:** *Angiogenesis, the physiological process through which new blood vessels form from pre-existing vessels, is essential for growth and development, but it also plays a critical role in pathological conditions such as cancer, diabetic retinopathy, and rheumatoid arthritis. Inhibiting angiogenesis is considered a promising therapeutic approach, particularly in cancer, where tumor growth and metastasis depend heavily on neovascularization. Natural plant-derived compounds have attracted significant interest in recent years due to their potential antiangiogenic properties and relatively low toxicity. Punica granatum (pomegranate) is a widely consumed fruit known for its antioxidant, anti-inflammatory, and anticancer properties, primarily attributed to its rich content of polyphenols, including punicalagins, ellagic acid, and anthocyanins.This study aims to evaluate the antiangiogenic activity of Punica granatum extract using the Chick Chorioallantoic Membrane (CAM) assay, a well-established in vivo model for studying angiogenesis. Fertilized chicken eggs were incubated and on the 7th day of embryonic development, sterile filter paper discs soaked in varying concentrations of pomegranate extract were placed on the CAM surface. After 72 hours of incubation, the CAMs were harvested and examined under a stereomicroscope to assess the degree of vascularization. Quantitative analysis was performed by counting the number of blood vessel branch points in treated versus control groups.The results showed a concentration- dependent inhibition of angiogenesis in the CAMs treated with Punica granatum extract. Higher concentrations of the extract resulted in a significant reduction in the number and complexity of blood vessels compared to the control group. This suggests that Punica granatum possesses potent antiangiogenic properties, potentially through the downregulation of pro-angiogenic factors or through antioxidant-mediated inhibition of endothelial cell proliferation and migration.*

**Keywords:** Punica granatum, angiogenesis, chorioallantoic Membrane Assay, antiangiogenic

## I. INTRODUCTION

Angiogenesis is the combination of two Greek word “Angion” and “Genesis” means “vase” and “the birth” respectively. This name is given to the particular growth of new blood capillaries from pre-existing blood vessels plexus. This process is essential to fulfill the nourishment and other damage of tissue. It is common and most important process in formation and development of vessels, so it is supportive in healing of wound granulation tissue.[1]

The anticancer effect of pomegranate fruit has been associated, at least in part, to a large number of biologically active phytochemicals which are present in the fruit. These effect of pomegranate fruit are considered due to their abilities to contract, disease and also repair damage due to antioxidative stress and inflammation. Tree, fruits, leaves and bark skin of this fruit have been used for various ailments and some other uses like in tanning industry.[2]

The various disease against which pomegranate extract is useful for prevention are prostate cancer, lymphoma, prostate hyperplasia, oxidative strees in diabetic hemodialysis, diabetes, rhinovirus infection and common cold, Acquired Immune Deficiency Syndrome (AIDS), cardiovascular protection and atherosclerosis.[3]


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Pomegranate fruit extract gives about 16% vitamin C of an adult's daily need. It consists of Potassium, Vitamin B5 and polyphenols which are tannins and flavonoids [4]. Pomegranate fruit extract is rich in polyphones which are hydrolysable tannins called elligitannins [5]. Other phytochemicals which are present in pomegranate contain gallocatechin, polyphenolic catechins and anthocyannins like delphinidins, prodelphinidin, pelargonidins and cyanidin[6]. To observe the development of blood vessels, Chick Chorioallantoic Membrane Assay model is very helpful to precede research as it is impossible in othermammalian system[7]. The Chorioallantoic membrane (CAM) is an extra developing membrane which is generally used in research studies of both processes angiogenesis and antiangiogenesis[8]. The evaluation of angiogenic and antiangiogenic effect of tested material can easily be done through CAM in short time of 24 hours[9], hence the model quickly and accurately explain both angiogenic and antiangiogenic characteristics of various chemical and natural extracts. Present study was aimed to identify the effect of Punica granatum fruit tincture on angiogenesis with the help of CAM (Chorioallantoic Membrane Assay).

**POMEGRANATE (Punica granetum L.):**

Pomegranate (Punica granetum L.) belong to the Punicaceae family. Its is specifically known for its nutritional & medicinal properties. Pomegranate is widely distributed around the world and therefore have the broad genetic diversity, resulting in differences in their phytochemical composition. The scientific community has has focused on positive health effect of pomegranate as a whole but the different varieties have rarely been compared according to their bioactive compounds and bioactivity.[10]

Plant Profile

Synonym:- Anar, Dalimb.

Biological Name:- Punica Granetum L. Family :- Punicaceae

Sugars (Fructose, Glucose), Pectin, Organic Acids, Flavonoids.

**CHEMICAL CONSTITUENTS OF POMEGRANATE:**

Chemical constituents which shows antiangiogenic activity are:

1. Luteolin
2. Quercetin
3. Kaempferol

**Luteolin**

It blocks the activation of VEGF receptor. The receptor which plays the vital role in angiogenesis and lymphangiogenesis (lymphatic vessels formation).

**Quercetin**

It shows action by inhibiting the signaling pathways VEGFR2, MEK/ERK, PI3K/AKT & MEK/JNK.

**Kamepferol**

Mainly targeted on VEGFR2 and inhibit angiogenesis

**Angiogenesis and Cancer: A Dynamic Interplay**

Cancer growth is intricately linked to angiogenesis. This phenomenon is not just a hallmark of cancer but a fundamental enabler of tumour survival and expansion. Tumours, much like normal tissues, require a steady supply of oxygen and nutrients to sustain their rapid proliferation. Angiogenesis fulfils this need by developing an extensive vascular network that infiltrates the tumour, providing the necessary sustenance and even a route for metastasis, where cancer cells spread to other parts of the body [14,15]. Over a dozen proteins and a variety of smaller molecules have been identified as "angiogenic" signals, released by tumours to kickstart angiogenesis. Key players in this process include VEGF and bFGF. These angiogenic factors act as growth signals, prompting endothelial cells to not only divide and move towards the source of the signal but also to transform into complex tubular structures essential for new blood vessel formation [16]. Tumour-induced inflammation and oxidative stress also participate in initiating pathological angiogenesis. When macrophages and neutrophils infiltrate the tumour microenvironment, they release pro-inflammatory cytokines,

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chemokines and Reactive Oxygen Species (ROS). These factors stimulate the production of angiogenic molecules, including VEGF and bFGF, leading to the development of abnormal vasculature. Furthermore, chronic inflammation and oxidative stress contribute to the creation of a hypoxic tumour environment, which activates signalling pathways like MAPK/ERK and stabilises hypoxia-inducible factor-1 alpha (HIF-1α), further upregulating the expression of angiogenic factors. This interplay between inflammation, oxidative stress and angiogenesis not only promotes tumour growth but also contributes to metastasis, becoming a significant area of study for developing anti-cancer therapies[17]

The concept of targeting angiogenesis for cancer therapy emerged in the 1970s, pi-oneered by Judah Folkman, who hypothesised that cutting off a tumour's blood supply could inhibit its growth. This revolutionary idea shifted the paradigm of cancer treatment, leading to the development of antiangiogenic drugs designed to thwart the formation of new blood vessels [18]. These therapies aim to starve the tumour by blocking the signalling pathways that promote vascular growth, such as the VEGF pathway. An example of an an-tiangiogenic agent used in clinical practice since 2004 is Bevacizumab (Avastin, developed by Genentech), a humanised recombinant monoclonal antibody directed toward VEGF (rhu Anti-VEGF Mab) [19]. Despite the theoretical promise of antiangiogenic strategies, their practical application has faced challenges [20]. One significant issue is that these therapies are often administered after cancer has already progressed, by which time the tumour has developed sophisticated mechanisms to adapt and survive. Additionally, tumours can become resistant to antiangiogenic treatments, finding alternative pathways to continue their growth and spread [21]. Moreover, the dynamic interplay between angiogenesis and cancer is not a one-way street. Tumours actively influence their surroundings, creating an environment that fosters angiogenesis. They release various growth factors and en-zymes that degrade the extracellular matrix, making it easier for new blood vessels to sprout. This bidirectional interaction highlights the complexity of the tumour mi-croenvironment and underscores the importance of understanding the various factors that promote or inhibit angiogenesis. It also emphasises the need for more nuanced approaches to overcoming cancer resistance mechanisms, particularly in relation to antiangiogenic therapies [22].

Recent research has also explored the potential of integrating antiangiogenic therapies with other treatment modalities. For instance, combining these therapies with immunother-apy, which harnesses the body's immune system to fight cancer, has shown promising results. By disrupting the blood supply to the tumour, antiangiogenic drugs can enhance the efficacy of immunotherapies, making it harder for the tumour to evade immune detection and destruction [23].

Bioactive Compounds in Pomegranate: Antiangiogenic and Therapeutic Potential

Pomegranate fruit is abundant in bioactive compounds that exhibit promising an- tiangiogenic properties. Notable molecules include ellagitannins (such as punicalagin, punicalin and ellagic acid), flavonoids including anthocyanins, flavonols (quercetin and kaempferol) and flavones (luteolin glycosides), fatty acids and polysaccharides. These compounds also exhibit antioxidant and anti-inflammatory activities, further contributing to their antiangiogenic effects [24].

**Flavonoids**

Flavonoids, abundant in vegetables, fruits and certain beverages, serve as potent sec-ondary metabolites with diverse health benefits. They exhibit antioxidant, anti-inflammatory, neuroprotective, cardioprotective, antiviral and antibacterial properties [25]. Notably, flavonoids are under investigation for their potential in cancer prevention by targeting endothelial cells and modulating angiogenesis. Indeed, several flavonoids have demon- strated efficacy in inhibiting angiogenesis and metastasis by regulating multiple signalling pathways. They affect the expression of key factors such as VEGF, bFGF, HIF-1α, MMPs and VEGFR, while also inhibiting NF-κB, PI3K/AKT/mTOR and MAPK/ERK signalling pathways.

Additionally, flavonoids play a role in adjusting endothelial cell proliferation and migration [26].

Kaempferol and quercetin, both flavonols present in pomegranate, exhibit signifi-cant anti- cancer properties. Kaempferol disrupts cancer cell VEGF release and reduces VEGF- stimulated cell viability by downregulating PI3K/AKT/mTOR and MAPK/ERK pathways [27]. Furthermore, kaempferol potentiates phosphorylation of endothelial Ni-tric Oxide Synthase (eNOS) and VEGFR-2 in endothelial cells [28]. Quercetin inhibits angiogenesis in human retinal endothelial cells by targeting the VEGFR2, MAPK/ERK, PI3K/AKT/mTOR and MAPK/JNK pathways

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[29]. Lastly, luteolin suppresses VEGF expression via HIF-1α- dependent mechanisms and inhibits ROS production [30]. It also reduces MMP-1 and MMP-9 expression, contributing to decreased angiogenesis in gastric cancer [31]. Pomegranate-derived oestrogenic flavonoids, including luteolin, quercetin and kaempferol, have been suggested to inhibit angiogenesis through multiple mechanisms. These include downregulating the expression of angiogenic growth factors, disrupting key cellular signalling pathways like PI3K/AKT/mTOR, and exerting antioxidant effects that reduce oxidative stress [32].

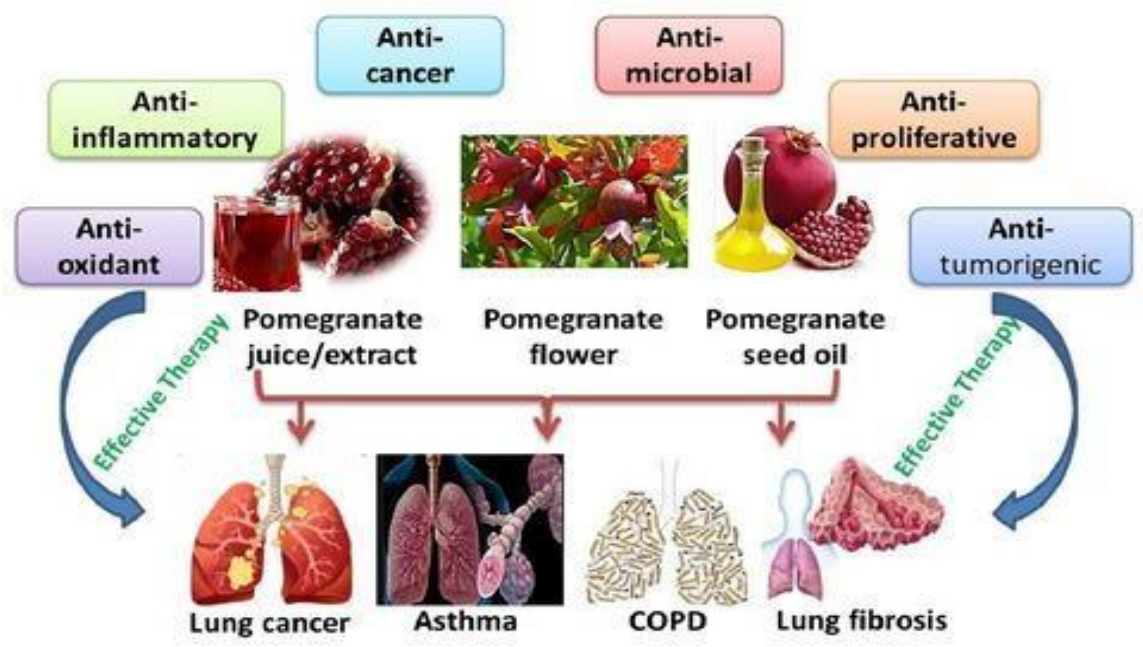


Fig.(1). Pomegranate Exhibiting Medicinal Properties

## II. METHOD AND MATERIALS

Method I: Tincturing fresh plant material when using 190 proof alcohol.

1. Chop the fresh plant into small pieces and stuff them into a canning jar, filling it to the top.
2. Pack the herb into the jar very tightly.
3. Get as much into the jar as you can, especially when working with a light herb.
4. Add 190-proof ethyl alcohol, filling the jar to the top. Make sure all hurb is covered by the alcohol.
5. Cap jar tightly.
6. Agitate the jar frequently for 14 days.
7. Decant the liquid, press the remaining wet pulp & combine these two liquid.
8. Filter if desired % Bottle, tightly cap and label.

Method II: Tincturing fresh plant material when using diluted alcohol (less than 190-proof).

1. Chop the fresh plant into small pieces and stuff them into a canning jar, filling it to the top.
2. Add menstruum (the easiest method to obtain is probably a commercial 80-proof or 100proof vodka. Eighty-proof vodka is approximately 40% alcohol by volume; 100 proof is approximately 50% alcohol by volume. 20-30% alcohol is sufficient to preserve a tincture. Therefore, when making a dried plant preparation, 80-proof vodka is adeduate. When making a fresh plant preparation, which always incorporates the juices of the plant [which dilute the menstruum], maybe 100-proof vodka is more judicious).

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3. Pour the entire ingredients (herb and menstruum) into a Vita-Mix or some other suitable blender and blend it like a smoothie. (you will have to make a large enough batch, so that the volume of menstruum required is sufficient to completely cover the blender blades).
4. Pour the liquefied ingredients into a jar and cap tightly.
5. Agitate tincture frequently for 14 days, then let it sit another day.
6. Decant, press filter % bottle tightly cap and label.[33]

**Day 01**

**Day 14**

**EVALUATION OF POMEGRANATE TINCTURE**

1. Organoleptic Test.

| Test | Observation | Inference |
|---|---|---|
| Colour | Slightly pink | Positive |
| Aroma | Fruity, characteristic smell | Positive |
| Taste | Astringent, slightly sweet | Positive |
| Sedimentation | Absent | Positive |
| Clarity | Clear or slightly cloudy | Positive |

2. Physicochemical Evaluation

| Parameter | Test | Result |
|---|---|---|
| pH | pH meter | 4.0 |
| Alcohol content(%) | Alcoholometry | 40% |
| Specific Gravity | Hydrometer | 1.5 |

3. Identification Test of Flavonoids

| Test | Observation | Inference | |
|---|---|---|---|
| 1. Shinoda test (Magnesium Hydrochloride Reaction) Sample+magnesium turning+conc.hcl | Appearance of reddish colour. | Confirm presence of Flavonoids. |  |
| 2. Alkali Reagent Test Leadacetate solution+sample | Formation of yellow colour . | Confirm presence of Flavonoids | |


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|---|---|---|---|
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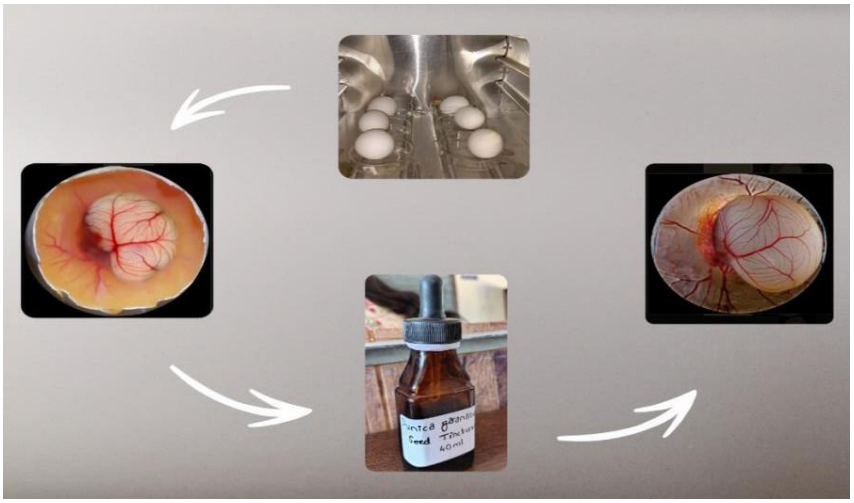
Test Observation Inference

1. Shinoda test (Magnesium Hydrochloride Reaction) Sample+magnesium turning+conc.hcl Appearance of reddish colour. Confirm presence of Flavonoids.
2. Alkali Reagent Test Leadacetate solution+sample Formation of yellow colour . Confirm presence of Flavonoids

## III. RESULTS

In the present study we have observed the effect of pomegranate on angiogenesis using chicken Chorioallantoic membrane (CAM) assay. After the application of pomegranate tincture decrease in formation of blood vessels was observed as compared to control group. When we applied tincture on CAM, these caused clear changes in blood vasculature of the CAM. Antiangiogenic activities (reduction in blood vessels) were seen after the introduction of fruit, which showed a perceptible reduction in the overall length and diameter.



Length of Blood Vessels(cm)

| Parameter | Group A | Group B | Group C |
|---|---|---|---|
| Controlled | 0.4231 | 0.6263 | 0.8323 |
| Treated | 0.4010 | 0.5925 | 0.7926 |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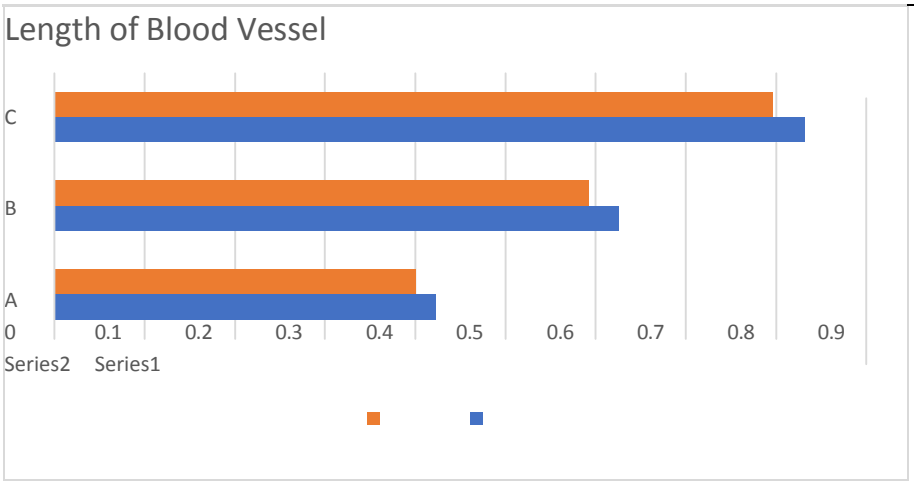


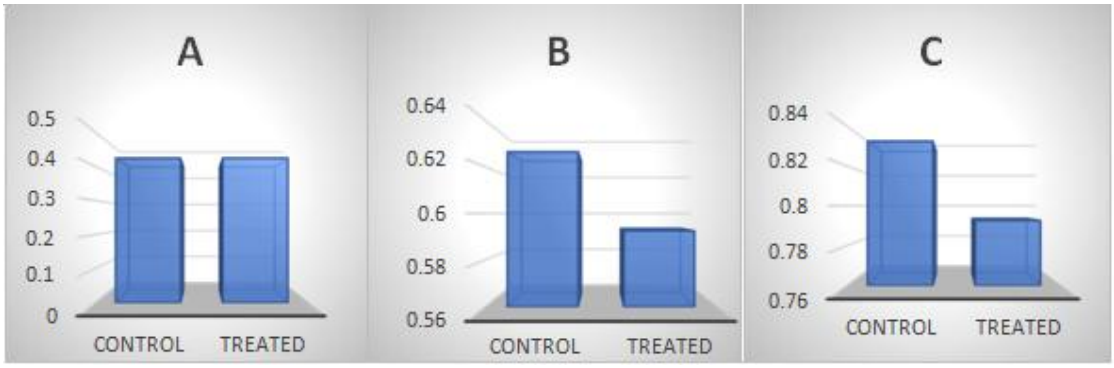


A B C

## III. CONCLUSION

Extensive evidence underscores the significant antiangiogenic potential of pomegranate extracts, positioning them as promising candidates for the prevention and treatment of cancer and other angiogenesis-related diseases. This potential is primarily attributed to their rich content of polyphenols, punicic acid and bioactive polysaccharides, which mod-ulate key molecular targets such as HIF-1α, VEGF, Sp, specific microRNAs and various inflammatory mediators. Beyond their antiangiogenic properties, the diverse bioactive compounds found in various parts of the pomegranate—such as juice, peels, kernels and roots—contribute to a wide range of biological activities, including anti-inflammatory, an-tioxidant and pro-apoptotic effects. These activities collectively inhibit neovascularization, potentially reducing tumour growth.

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