

Pomegranate and Cancer: Recent Research on Punica Granatum (Pomegranate) and Ellagic Acid

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Theme: [Science and Medicine](#)

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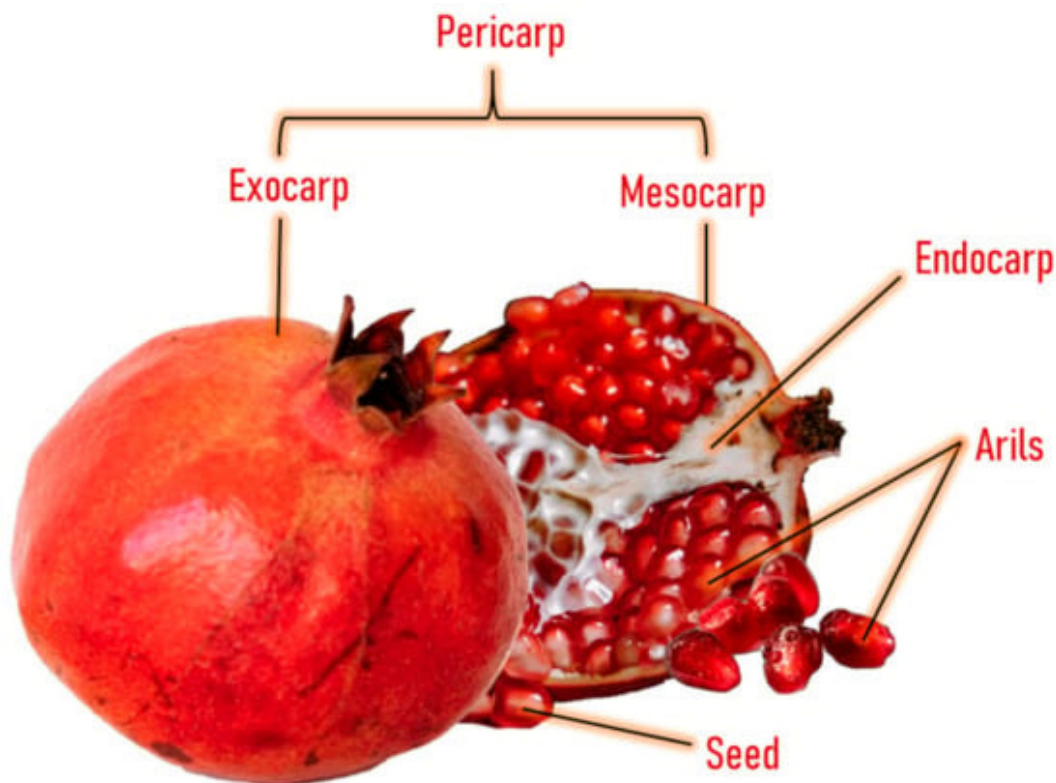
Papers reviewed:

- [2021 Aug \(Wong et al\)](#) - Pomegranate bioactive constituents target multiple oncogenic and oncosuppressive signaling for cancer prevention and intervention
- [2022 Feb \(Cheshomi\)](#) - The effects of ellagic acid and other pomegranate (*Punica granatum* L.) derivatives on human gastric cancer AGS cells
- [2023 Jan \(Teniente et al\)](#) - Anticancer Effect of Pomegranate Peel Polyphenols against Cervical Cancer
- [2023 Apr \(Habchi et al\)](#) - Determination of the Antioxidant and Antiproliferative Properties of Pomegranate Peel Extract Obtained by Ultrasound on HCT-116 Colorectal Cancer Cell Line
- [2023 July \(Rahman et al\)](#) - Pomegranate-specific natural compounds as onco-preventive and onco-therapeutic compounds: Comparison with conventional drugs acting on the same molecular mechanisms

[2021 Aug \(Wong et al\)](#) - Pomegranate bioactive constituents target multiple oncogenic and oncosuppressive signaling for cancer prevention and intervention

- Research on pomegranate (*Punica granatum* L.), a fruit of the Punicaceae family, has shown enormous potential for cancer prevention and intervention
- In addition to a rich source of polyphenols in its juice, including flavonoids and ellagitannins, pomegranate also houses hundreds of other phytochemicals in its pericarp, seed, flower, bark, flowers and leaves.

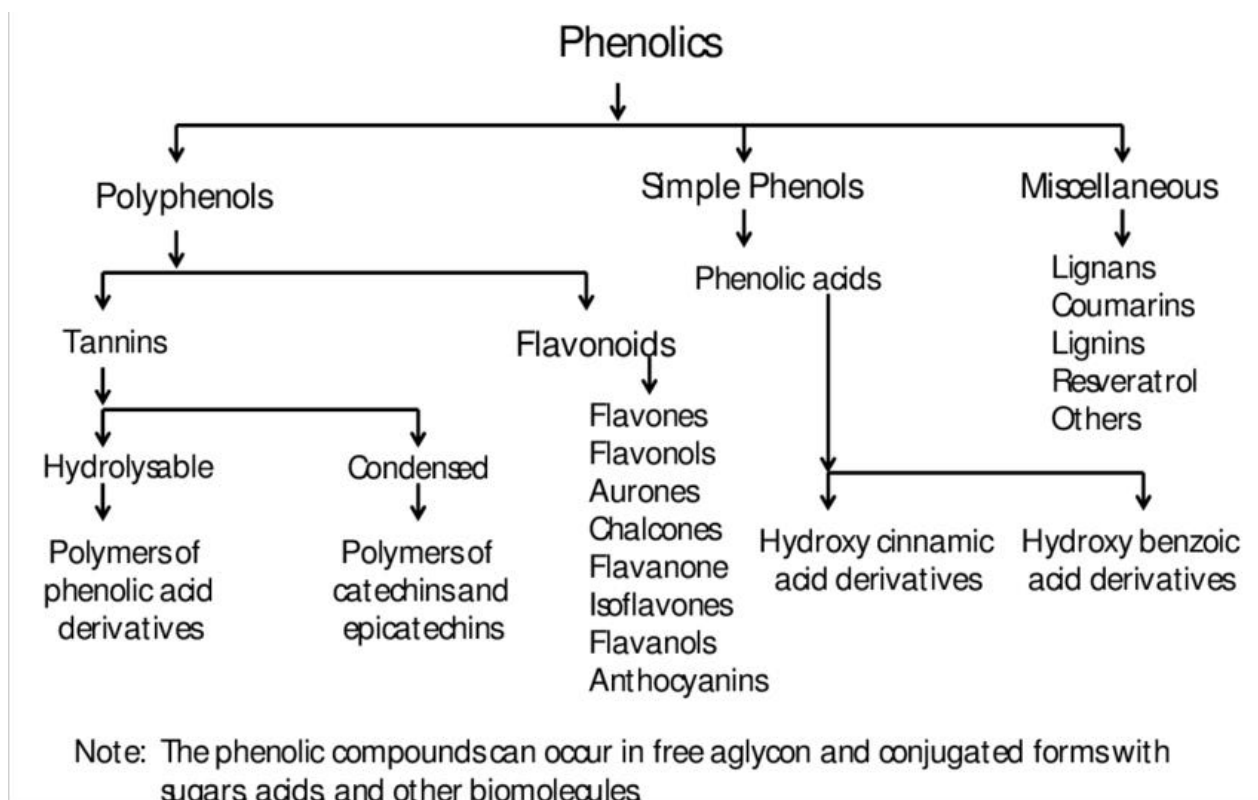
- **Pomegranate (*Punica granatum*, L.), a fruit-bearing deciduous large shrub or small tree, is a native of the Himalayas in northern India to Iran**
 - Now cultivated globally, India and Iran are the leading pomegranate producing countries
 - In the United States, the primary production sites are the drier regions of Arizona and California
 - The shrub grows from 5 to 10 m in height
- **Pomegranate fruit** (classified as a large berry) ranges in color from light red to a green-yellow or purple. The fruit can be 5-20 cm in diameter, about 200-800 g in weight, grenade-shaped and crowned by the pointed calyx
 - It contains approximately 200-1400 white, red or purple **arils** embedded into a spongy, white membrane enveloped by exocarp.
- **pomegranate fruit contains three parts:**
 1. **seeds** (3% fruit weight) containing about 20% oil,
 2. **juice** (30% fruit weight) and
 3. **peels (pericarp)** that include interior network of membranes



- pomegranate fruit used for medicinal purposes in ancient cultures for centuries
- pomegranate fruits are widely consumed in fresh and beverage forms as juice as well as jam, jelly and wine
- **pomegranate leaves are brewed as tea** and dried seeds are used as spice
- pomegranate features prominently in various major world religions, such as Buddhism, Christianity, Islam, Judaism, and Zoroastrianism
- It represents a symbol of life, longevity, health, femininity, fecundity, knowledge, morality, immortality and spirituality
- In the Ancient Greek myth of Persephone's abduction, the pomegranate, known as the "fruit of the dead," **signifies life and rebirth**
- applications of pomegranate are expansive and have notable uses in both

Ayurvedic and the Unani systems of medicine.

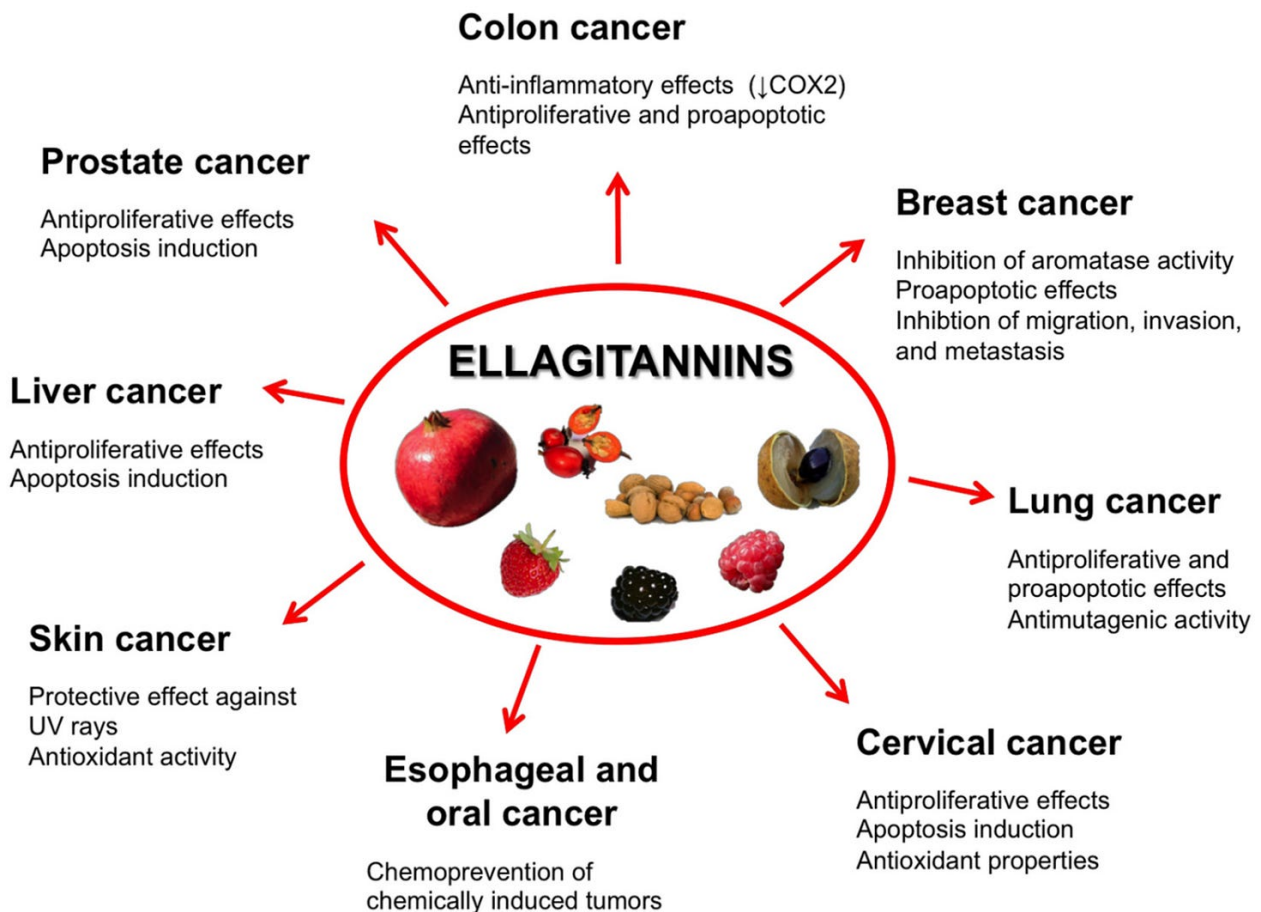
- In Ayurveda (India), pomegranate is regarded as a “pharmacy unto itself”



Bioactive Compounds

- **Peel (pericarp)** - half of the fruit weight, has important compounds - **phenolics, flavonoids, ellagitannins, proanthocyanidin**
 - phenolic acids (eg caffeic acid), ellagitannins
 - flavonoids: kaempferol, Quercetin, catechin, EGCG
- **arils (edible parts)** - 85% water, 11% sugars, 1.4% pectin, organic acids, anthocyanins
 - **pomegranate juice** - rich source of ellagic acid
- **seeds** - high concentration of lipids but lack polyphenols, have **ellagic acid derivatives, triterpenoids, sterols**
- **leaves** - contain ellagitannins, and various phytochemicals and flavone glycosides
- **root** - alkaloids
- **bark** - alkaloids, ellagitannins
- **flowers** - hydroxybenzoic acids, triterpenoids

Pomegranate and Cancer



Source: [\(2016 Ismail\)](#)

- **Breast Cancer** - extensively studied

- fermented juice polyphenols have superior antiproliferative effect to fresh juice polyphenols
- pomegranate fruit extract **inhibits NF-κB activation**
- pomegranate fruit juice inhibits metastasis (EMT, adhesion, migration)
- whole fruit extract induced **Cancer Stem Cell differentiation and inhibited EMT and cancer cell migration, inhibited VEGF**
- **ellagitannins** have anti-aromatase activity in ER-positive breast cancer
- pomegranate fruit extract **enhances action of tamoxifen** in sensitive and tamoxifen-resistant cells
- **fruit peel extract**, containing **ellagitannins** and free **ellagic acid** (most abundant phenolic acid) showed antioxidant and proapoptotic effects (inhibit proliferation via cell cycle arrest & apoptosis)
- **pomegranate seeds** (linolenic acids) decrease cell viability, inhibit VEGF
- **in vivo (mice)** - fermented juice polyphenols 50% inhibition of breast ca lesions and pomegranate seed oil caused 90% reduction of breast tumors
 - pomegranate juice fed for 35 days reduced tumor size & volume (high apoptosis, inhibited VEGF, NF-κB, Akt, PI3k)
 - Expression of micro RNAs (miRNA) significantly reduced

- **Colon Cancer** – pomegranate juice (ellagitannins) and total pomegranate tannin extract have cytotoxic effects on in vitro colon cancer cells (cell cycle arrest, inhibited VEGF, NF-κB, Akt, PI3k, increased miRNA-126).
 - **pomegranate peel polysaccharide** – induced apoptosis of colon cancer cells
 - **pomegranate peel punicalagin (ellagitannin) & ellagic acid** – induced apoptosis, cell cycle arrest
 - **pomegranate seed oil** – in vivo – mice had reduced incidence of colon tumors
 - **pomegranate peel extract** – in vivo – rats had higher antioxidants, prevented colon tumor formation
 - **pomegranate fruit extract** – in vivo – rats had longer survival, lower tumor incidence and reduced carcinoembryonic antigen (CEA).

Summary for in vivo animal studies:

- Breast cancer, colon cancer, lung cancer, liver cancer, skin cancer, bladder cancer, prostate, ovarian
- Pomegranate: juice, peel extract, seed oil, emulsion
- Anti-cancer effects: **reduced incidence, reduced tumor volume, size and weight**
- Mechanisms: **↑Apoptosis, ↓proliferation, ↓NF-κB, ↓VEGF, ↓MMP**

Human Clinical Trials

- There have been a dozen Human clinical trials
- Breast cancer – Phase I/II – pomegranate juice, drank it for 3 weeks – significant decline in estrone (promotes tumor growth) (mild effect)
- Colon cancer – Phase I/II – pomegranate extracts (ellagic acid, punicalagin, punicalin) (900mg/day for 15 days) – modulation of many micro RNAs (moderate effect)
- Prostate cancer – Phase II – pomegranate juice or extract (consumed daily up to 4 years) – significantly prolonged PSA doubling time, decreased PSA in 13% (mild effect)
 - 2014 Thomas et al – used a polyphenol rich whole food supplement (pomegranate whole fruit powder, turmeric, broccoli, green tea extract) for 6 month – significant suppression of rising PSA levels.
 - Conclusion: “Therapeutic potential of pomegranate in prostate cancer continues to be controversial”

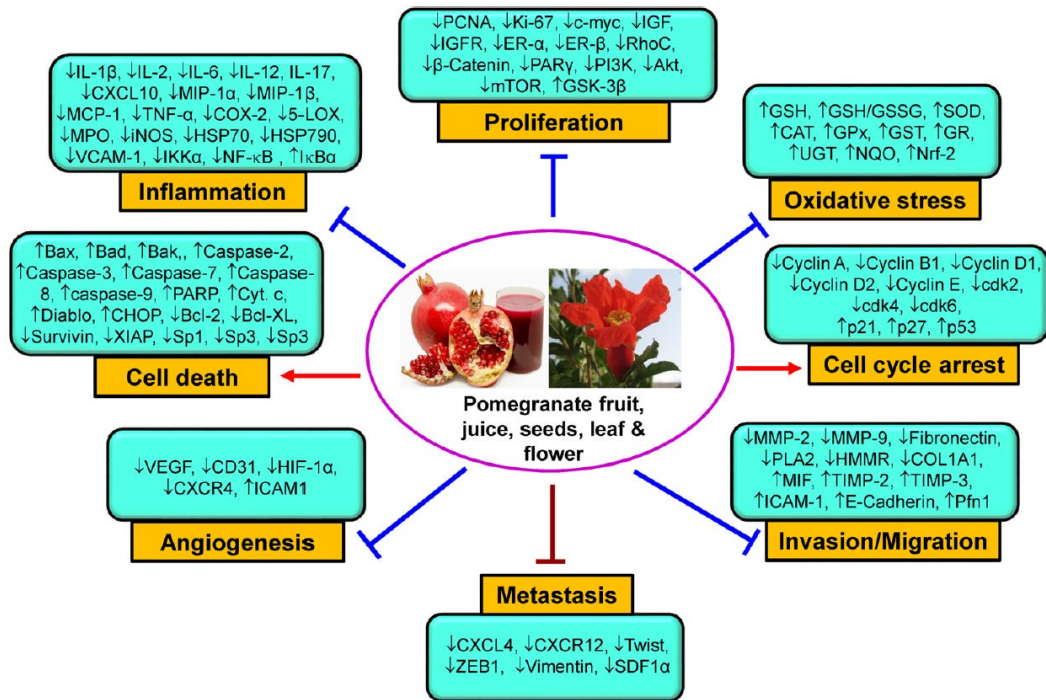


Fig. 8. Major anticancer mechanisms and molecular targets of pomegranate-derived constituents based on *in vitro* and *in vivo* studies.

Bioavailability

- **ellagic acid** – detected in plasma at 1hr after eating, gone by 4hr (halflife 0.7hr)
- **ellagitannins** – none detected in plasma at 1hr after eating but...
 - ellagitannins released ellagic acid in the jejunum, metabolized to **urolithins** which persist for long periods of time (may be responsible for therapeutic effects)
- **“major pomegranate phytochemicals are absorbed from the gastrointestinal tract and become bioavailable”**
- “main metabolic products of ellagitannins appear to be urolithins which are formed by gut microflora and the difference in gut microflora also explain the contrasting concentrations and the rate of formation in individuals”
- **“metabolites of ellagitannins may be responsible for the long-term therapeutic effects of pomegranate, including its anticancer potential”**

Safety

- pomegranate juice consumption in prostate cancer patients – no adverse effects
- pomegranate peel extract up to 3 gram doses – no adverse effects
- mild side effects include nausea, diarrhea

Conclusion

- “Known as “a phytochemical reservoir of heuristic medicinal value”, pomegranate has acquired a prominent role in traditional medicines for the treatment of various disorders”
- **“The full potential pomegranate in cancer prevention and therapy as well as its molecular targets in cancer are not completely understood”**
- “pomegranate’s phytochemicals not only act synergistically with its own phytochemicals, but also with other phytochemicals and even with other

established chemotherapeutic drugs to confer superior anticancer action to that of any single compound”

- “many studies reported no significant differences between pomegranate-treated and placebo groups. Yet subsequent subgroup analysis has reported significant effect with pomegranate therapy, thus suggesting that certain population of cancer patient may benefit more from pomegranate’s therapeutic activity”
- **“Few clinical studies are conducted with limited sample size and cancer endpoints”**

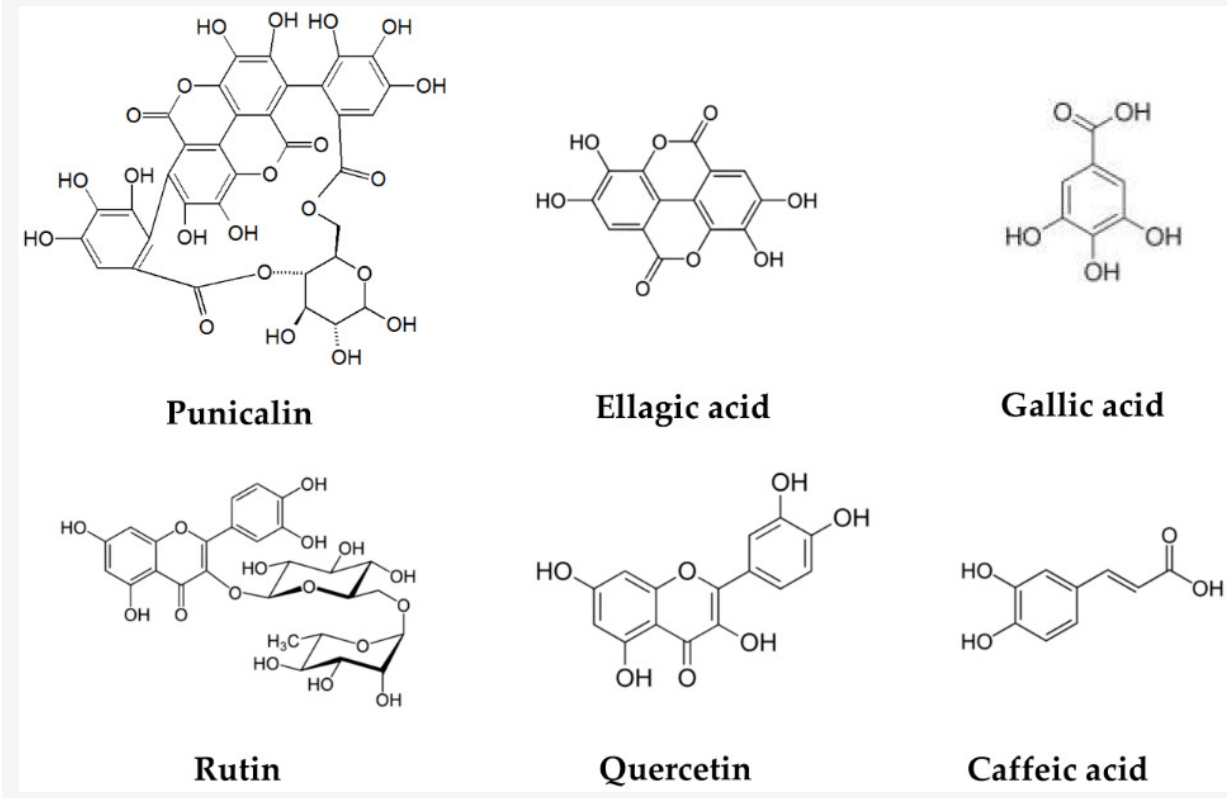
2022 Feb (Cheshomi) - The effects of ellagic acid and other pomegranate (*Punica granatum* L.) derivatives on human gastric cancer AGS cells

- **pomegranate fruit juice (PFJ)**, thanks to its rich polyphenolic composition, can have anti-cancer activity against several human malignancies such as prostate, colon, liver, and breast cancer
- **pomegranate peel extract (PPE)** - also has a high content of polyphenolic compounds and therefore, it can induce cell death in various cancers including breast, melanoma, and colon
- **ellagic acid** - as one of the main polyphenols in PFJ and PPE, can have significant anti-tumor effects on different human cancers including bladder, blood, breast, cervical, colorectal, liver, pancreas, and prostate cancer
 - ellagic acid caused more drastic changes in expression of desired genes than PFJ or PPE (dose dependent)
 - **ellagic acid increases expression of p53**
 - ellagic acid significantly alters expression of all studied genes, while PPE only affects some.
 - ellagic acid could exhibit an anti-inflammatory effect through down-regulating iNOS, TNF- α , and IL-6 via NF- κ B inhibition
 - in vivo (gastric cancer mice) - ellagic acid suppressed tumor growth and reduced final tumor volume in a **dose-dependent manner**
 - **there are higher levels of ellagic acid in peel than in juice**
- Conclusion: “Our results revealed that in the case of gastric cancer, **EA in comparison to PFJ and PPE, had far more significant anti-cancer effects** in several aspects such as apoptosis induction, reducing cell migration, altered expression of genes associated with programmed cell death, reduced expression of inflammatory genes, as well as inhibition of tumor growth in mice.”

2023 Jan (Teniente et al) - Anticancer Effect of Pomegranate Peel Polyphenols against Cervical Cancer

- Pomegranate peel extract is an excellent source of polyphenols, such as **punicalagin, punicalin, ellagic acid, and caffeic acid**
- These phenolic compounds have antineoplastic activity in in vitro models of cervical cancer through the regulation of cellular redox balance, induction of apoptosis, cell cycle arrest, and modulation of signaling pathways

Figure 2. Chemical structures of polyphenols present in pomegranate peel.



- **pomegranate peel** has a significant amount of protein, polysaccharides, minerals (calcium, phosphorus, magnesium, potassium, sodium), and phenolic compounds such as flavonoids (catechin, epicatechin, quercetin, rutin, kaempferol, hesperidine, anthocyanins, procyanidins), hydrolyzable tannins (pedunculagin, punicalin, punicalagin), and phenolic acids (gallic, ellagic, vanillic, caffeic, ferulic, cinnamic, *p*-coumaric acids)
- **Punicalagin (PCN)**, a hydrolyzable tannin present in pomegranate peel, provides numerous beneficial properties and is associated with anticancer activity in in vitro models because it intervenes in the cell cycle, proliferation/survival signals, and catabolic processes such as apoptosis and autophagy
 - **authors observed an increase in ROS generation and alterations in mitochondrial membrane potential, causing a cytotoxic effect on cervical cancer cells.**
 - **Also downregulated expression of NF-κB and upregulated expression of p53 mRNA, stimulating apoptosis**
 - Punicalagin showed dose dependent inhibition of viability of HeLa cells, due to cell cycle arrest, apoptosis.
- **Punicalin** - another hydrolyzable tannin - demonstrates various therapeutic properties, including antioxidant, anti-inflammatory, hepatoprotective, antiviral, antibacterial, and anticancer activities
 - treatment with **punicalin in conjunction with ellagic acid (EA)** (extracted and purified from pomegranate peel) had a dose-dependent cytotoxic and antiproliferative effect on HeLa cells.
 - inhibited Akt/mTOR pathway
- **Gallic acid (GA)** is a polyphenol found in the peel and arils of pomegranate.
 - has potent antioxidant, anti-inflammatory, antimutagenic, and

- ant anticancer activities
 - causes increase in ROS, decrease in Akt, EGFR
- **ellagic acid** – another polyphenol found in pomegranate peel
 - ellagic acid causes dose and time dependent decrease in viability of cervical cancer cells
 - increase in ROS and DNA damage (cell death), **increase in p53 and p21.**
- **Caffeic acid (CA)** is a phenolic compound found in pomegranate peel and juice
 - Different studies have reported its antioxidant, anti-inflammatory, antihypertensive, antidiabetic, and anticancer properties
 - cell cycle arrest, apoptosis
 - **metformin + caffeic acid** – synergistic antimetastatic effect.
- **chlorogenic acid** – another polyphenol (also found in coffee beans)
 - when combined with other polyphenols, apoptotic effect was more significant than by itself.
- **Delphinidin (DPN) is an anthocyanidin found in the peel, arils, and juice of pomegranate.**
 - Its anticancer activity has been observed in liver, breast, ovarian, lung, and cervical cancer cell lines
 - dose dependent apoptotic effect
- Conclusion: **“pomegranate peel polyphenols seem to be a viable alternative for the prevention and treatment of cervical cancer.”**
- “Recent studies have demonstrated that pomegranate peel polyphenols, independently or in combination with other compounds or drugs, possess antiproliferative activities in cervical cancer models through the induction of apoptosis, cell cycle arrest, inhibition of DNA synthesis, and modulation of different signaling pathways”

2023 Apr (Habchi et al) - Determination of the Antioxidant and Antiproliferative Properties of Pomegranate Peel Extract Obtained by Ultrasound on HCT-116 Colorectal Cancer Cell Line

- industrial processing of pomegranate fruits results in huge amounts of by-products, such as the pomegranate peels, which are regarded as waste in the food industry.
- beside the pomegranate fruit itself, **this non-edible part of pomegranate has been shown to be rich in bioactive molecules** that are responsible for bio activities, such as antimicrobial, antioxidant, anti-inflammatory, anticancer activities
- tests in this study showed presence of **phenols, flavonoids, terpenoids, sterols and steroids, alkaloids**, reducing sugars, and proteins in ethanolic extracts of pomegranate peels
- **phenolic compounds (total of 8) and flavonoids (total of 6) in pomegranate peels** are able to scavenge free radicals, and their abundance in an extract contributes to its antioxidant activity.
- **pomegranate peel extracts** – in colorectal cancer, down-regulate the Wnt pathway, inhibit stem cells, inhibit angiogenesis, inhibit migration, etc.
- Conclusion: **“pomegranate peel, which is considered as a food-waste, is**

rich in bioactive molecules that are effective for the treatment of colorectal cancer.”

2023 July (Rahman et al) - Pomegranate-specific natural compounds as onco-preventive and onco-therapeutic compounds: Comparison with conventional drugs acting on the same molecular mechanisms

- Pomegranate was first planted in what is now Iran, but it has also been grown in Northern India and across the Mediterranean area for a very long time
- Because of the presence of hydrolyzable substances in huge quantities, such as anthocyanins and tannins in pomegranate seeds, they are easily digested and have powerful anti-inflammatory and antioxidant qualities
- Pomegranate antioxidant and polyphenol combinations seem to offer a larger range of activity against a variety of free radicals
- **Pomegranate anthocyanins are known to have a much higher level of antioxidant activity compared to the antioxidants found in green tea and red wine**
- Pomegranate juice’s polyphenolic concentration gives it **more antioxidant action compared to green tea and red wine**
- **Peel, mesocarp, and arils** include hydroxybenzoic acids, gallagyl esters, gallotannins, anthocyanins, ellagitannins, and hydroxycinnamic acids.
- **“Because most of the phenolic compounds in pomegranate fruit are concentrated in the peel and pericarp,** commercial juices produced by squeezing the whole fruits contain large quantities of **gallic acid, punicalagin, and ellagic acid,** in comparison to hand-squeezed smoothies made from the arils alone”
- **Punicalagin,** the most frequent pomegranate ellagitannin, ranges from 11 to 20 g/kg in the peel and mesocarp and 4–565 mg/L in the juice
 - Punicalagin and ellagic acid are the principal phenolic components in the peel extract.
 - Punicalagin is also the primary component in the pomegranate juice
 - **Punicalagin inhibits NF-κB, mTOR and MAPK pathways**
- **ellagitannins** – pomegranate’s antioxidant action is connected to its polyphenolic compounds, especially **ellagitannins**
 - bioavailability of dietary ellagitannins is not properly elucidated
 - **ellagitannins absorption, plasma clearance, and urolithin metabolites excretion is prolonged for two days following pomegranate juice consumption**
 - **these compounds exhibited antioxidant and anti-inflammatory activities**
 - Animal models absorb urolithin metabolites, which accumulate in the colon, prostate, and other tissues
- Pomegranate fruit, juice, seed, and seed oil were all found to be beneficial.
- **Punicalagin and ellagic acid** are the principal phenolic components in the peel extract, inhibit mTOR pathway
- “Pomegranate is an excellent source of polyphenols, including ellagitannins like punicalagin and punicalin and flavonoids like quercetin and kaempferol”

- “Pomegranate juice is also a good source of flavonoids. The compounds **punicalagin and punicalin**, which may be found in both the juice and the peel of pomegranate, have the ability to block the AKT pathway in cancer cells
- **breast cancer - Pomegranate seed oil** and **fermented fruit extracts** were shown to reduce the number of tumors produced during in vivo investigations on mammary organ culture in mice
 - Cell growth was shown to be inhibited by ellagic acid, ursolic acid, luteolin
- **colon cancer** - ellagitannin and urolithin impede colon cancer cell growth.
 - achieved by cell cycle arrest and blocking MAPK pathway
- Conclusion: “Oral pomegranate extract alters cancer-related molecular markers, validating preclinical results. However, it has been shown in several randomized controlled studies that **pomegranate treatment does not significantly outperform placebo**. Later subgroup research showed that pomegranate treatment **might help certain cancer patients more than others**”
- “In vivo and in vitro testing pointed to the safety of pomegranate products.”

My Take...

Pomegranate is a fruit that is very rich in cancer fighting compounds.

It seems the Pomegranate peel extract has the most anti-cancer polyphenols, although the pomegranate fruit juice and pomegranate seed oil have many anti-cancer bioactive compounds as well.

The topic is quite complicated and medical literature very difficult to digest.

In an “Alternative Cancer Treatment” plan, Pomegranate fruit juice fits into the category “Bioactive Compounds - food” while Pomegranate peel extract is in the “Bioactive Compounds - supplements” category.

TURBO CANCER TREATMENT:

Repurposed Drugs – Ivermectin, Fenbendazole, Mebendazole

Bioactive compounds (supplements) - IP6, CBD (Cannabidiol), Quercetin, Olive Leaf (Oleuropein), Bromelain, Green Tea Extract (EGCG), Curcumin, Resveratrol, Berberine, Black Seed Oil (Thymoquinone)

Bioactive compounds (mushrooms) – Turkey Tail, CHAGA, Reishi, Shiitake, Maitake, Lion’s Mane, Cordyceps

Bioactive compounds (foods) – garlic, ginger, apricot seeds, soursop fruit, noni fruit, green barley grass, pomegranate, Oregano oil, (fermented foods – kimchi, sauerkraut, miso, noni)

**Immune Support – Vitamin D/K2, Melatonin, Selenium
Ketogenic Diet
3-5 day FASTING**

The animal and in vitro studies show very dramatic anti-cancer effects, while the human trials show only mild or modest anti-cancer effects so far.

Best studied cancers with human trials: breast cancer, prostate cancer, colon cancer.

In vivo mouse studies: Breast cancer, prostate cancer, colon cancer, lung cancer, liver cancer, skin cancer, bladder cancer, ovarian, cervical, thyroid cancer.

In vitro cell studies: pancreatic, oral, leukemia, gastric, renal, endometrial, gliomas.

For maximum benefit, you want to consume either the pomegranate peel extract or pomegranate whole fruit juice (rather than juice made from arils only).

Another interesting product is the pomegranate seed oil.

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***Dr. William Makis** is a Canadian physician with expertise in Radiology, Oncology and Immunology. Governor General’s Medal, University of Toronto Scholar. Author of 100+ peer-reviewed medical publications.*

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