

The beneficial effects of pomegranate (*Punica granatum L.*) consumption on human health: a review.

Authors: Agnese Di Napoli^{1,2}, Federico Germani¹, Francesco Parisi² and Pietro Zucchetti¹

¹ Istituto Italiano di Permacultura, Loc. Gambaldo n.1 Via Torino, 12070 Scagnello (CN), Italy.

² DNA Prolife Srls Unipersonale, Via S. Allende 31, 50032 Borgo San Lorenzo (FI), Italy

Corresponding author: Agnese Di Napoli, Istituto Italiano di Permacultura, Loc. Gambaldo n.1

Via Torino, 12070 Scagnello (CN), Italy. E-mail: agnesedinapoli@outlook.com

Abstract

The pomegranate (*Punica granatum L.*) is a small tree or shrub, which is grown in large parts of the world. The medicinal properties of this plant are known since ancient times and are due to the phytochemical constituents found in the plant. This review describes the therapeutic effects of pomegranate, which are reported in the scientific literature. We performed a literature search, using the PubMed database. We utilised this database to find the research articles published between 2000 and 2021, showing the medicinal properties of oral intake of pomegranate. We included 55 research articles and we found 11 beneficial effects of pomegranate consumption on human health. The therapeutic effects of this plant comprise those on diabetes, the cardiovascular system, oxidative status, the nervous system, cancer, colitis, metabolic syndrome and obesity, arthritis, the reproductive system, parasitic infections and skin health. Cardiovascular, antioxidant and antidiabetic activities are well reported in the scientific literature and the medicinal properties of pomegranate may be exerted by polyphenols found in the plant. This review shows the health benefits of oral intake of pomegranate. The most commonly reported beneficial activities of this plant are antioxidant, cardiovascular and antidiabetic effects. The polyphenol constituents of pomegranate may be responsible for its medicinal properties. Future research is needed to define the therapeutic effects of oral intake of this plant and the phytochemical compounds implicated in these activities.

Keywords: Pomegranate, Polyphenols, Therapeutic effects, Antioxidant, Cardiovascular, Antidiabetic

1. Introduction

The pomegranate (*Punica granatum L.*) is a shrub or small tree widely spread in Iran and South Asia and commonly cultivated in many parts of the world (e.g., the Mediterranean region, South Africa, North and South America, Australia, Japan and China) (Magangana *et al.*, 2020; Viuda-Martos *et al.*, 2010). "*Punica*" comes from the latin words "*Punicum malum*", which mean "the Carthaginian apple". The latin word "*granatum*" means "seeded" (Grieve, 1931). *P. granatum* belongs to the Myrtales order and is considered a member of the family Lythraceae or Punicaceae (Kandylis and Kokkinomagoulos, 2020). The plant can reach minimum and maximum heights of 1 and 10 meters, respectively, and can live up to 300 years (Levin, 2006). The pomegranate leaves are elongated and bright-green. The orange-red flowers are flashy and have a bell-shaped calyx. The pomegranate fruit is round, ranges from 8 to 18 cm in diameter, has a leathery rind and a calyx at the top. Fruit skin colour changes from green to yellow to red. The edible seeds and juice are enclosed in arils, which are located inside the fruit (Grieve, 1931; Jurenka, 2008; Levin, 2006; Zarfeshany *et al.*, 2014) (Fig. 1).

[Insert Fig. 1 here]

The pomegranate is characterized by high nutritional value due to metabolites found in different parts of the plant, such as flowers, leaves, peel, seeds, juice, roots and bark. Sugars (e.g., fructose and glucose), organic acids (e.g., citric acid), dietary fibres, proteins, lipids and bioactive compounds are mainly found in pomegranate (Bar-Ya'akov *et al.*, 2019). Various phytochemicals are present in different parts of the plant and are considered responsible for its therapeutic effects, which are known since antiquity (Longtin, 2003). Phytoestrogens and punicic acid are present in seeds (Shabbir *et al.*, 2017; Zarfeshany *et al.*, 2014) (Fig. 2). The pomegranate is a rich source of polyphenols. The main flavonoids include anthocyanins, luteolin,

kaempferol and quercetin. Anthocyanins, which are plant pigments, are found in peel, juice, flowers and leaves. Ellagitannins and gallotannins are hydrolyzable tannins (e.g., punicalagin, ellagic acid, punicalin and gallagic acid) present in every part of the plant (Fig. 3). Alkaloids are mainly found in roots and bark (Bar-Ya'akov *et al.*, 2019; Sreekumar *et al.*, 2014).

[Insert Fig. 2 and Fig. 3 here]

The pomegranate is consumed mainly as fruit, fresh juice, concentrated syrup, jelly, sauce, jam, tea infusion and plant extracts (e.g., capsules and tablets) (Zarfeshany *et al.*, 2014). The consumption of pomegranate has spread worldwide and many research studies have reported experimental evidence on the health benefits of this plant. In this review, we perform a literature search to find the beneficial effects of oral consumption of pomegranate. This study can help improve our knowledge of the therapeutic effects of this plant and its use for preventing and treating different health conditions.

2. Methods

We used the PubMed database (www.ncbi.nlm.nih.gov/pubmed) to find previous research studies, which described the therapeutic effects of pomegranate consumption. We set the following PubMed options: article type (books and documents, clinical trial and randomized controlled trial), language (English) and publication date (2000 to 2021). We entered six keywords into the database: "*Punica granatum*", "pomegranate", "*Punica granatum* therapeutic effects", "*Punica granatum* health benefits", "*Punica granatum* medicinal properties" and "*Punica granatum* therapeutic properties".

After performing the search by keywords, we read the titles and abstracts of the articles and we chose those related to the beneficial effects of pomegranate consumption on human health. Then we read them carefully and we selected the appropriate research articles.

3. Results

Overall, we found 125 research studies, carrying out the literature search, and we selected 55 articles, which were suitable for defining the medicinal properties of pomegranate consumption. We describe 11 therapeutic effects of oral intake of pomegranate, which are reported in previous research studies. Our results show that oral consumption of pomegranate exerts beneficial effects on the nervous system, oxidative stress, the reproductive system, colitis, cancer, the cardiovascular system, diabetes, obesity and metabolic syndrome, parasitic infections, arthritis and skin health (Table 1).

[Insert Table 1 here]

3.1. Neuroprotective activity

A study by Siddarth *et al.* (2020) showed that daily consumption of pomegranate juice over a period of 1 year can exert beneficial effects on visual memory in aging individuals. Another study found that maternal intake of pomegranate juice exhibits neuroprotective effect in newborns with intrauterine growth restriction (IUGR) (Matthews *et al.*, 2019). Bellone and colleagues (2019) showed that pomegranate polyphenol supplements enhance functional and cognitive outcomes in post-stroke rehabilitation.

3.2. Antioxidant activity

A previous study by Urbaniak *et al.* (2018) found that daily oral intake of pomegranate juice increases total antioxidant capacity (TAC) in athletes (i.e., rowers). Mazani and colleagues

(2014) demonstrated that consumption of pomegranate juice limits oxidative damage after exhaustive exercise. Previous research showed that punicalagin present in pomegranate juice has antioxidant activity in human placenta *in vivo* and *in vitro* (Chen *et al.*, 2012). Another study demonstrated that consumption of probiotic pomegranate juice improves antioxidant activity in women with polycystic ovary syndrome (PCOS) (Esmaeilinezhad *et al.*, 2019; Esmaeilinezhad *et al.*, 2020). A study by Heber *et al.* (2007) found that oral consumption of ellagitannin-rich pomegranate extract exerts antioxidant effects in overweight individuals. Another study found that oral intake of pomegranate extract reduces oxidative stress in overweight or obese individuals (Hosseini *et al.*, 2016). Gouda and colleagues (2016) showed improved antioxidant activity in human plasma and urine after daily consumption of polyphenol-rich pomegranate juice. Other two studies showed the antioxidant activity of pomegranate juice in diabetic individuals (Rosenblat *et al.*, 2006; Sohrab *et al.*, 2017). Ghoochani and colleagues (2016) found the antioxidant activity of pomegranate juice in patients with osteoarthritis (OA), while other two studies demonstrated that consumption of pomegranate extract has antioxidant activity in patients with rheumatoid arthritis (RA) (Balbir-Gurman *et al.*, 2011; Ghavipour *et al.*, 2017). Previous studies showed improved oxidative status in individuals undergoing hemodialysis and drinking pomegranate juice three times per week (Barati Boldaji *et al.*, 2020; Shema-Didi *et al.*, 2012) or during a single session (Shema-Didi *et al.*, 2013). Another study demonstrated that pomegranate polyphenol extract has beneficial effects on oxidative stress in hemodialysis patients (Wu *et al.*, 2015). Guo and colleagues (2008) found increased antioxidant activity after daily oral intake of pomegranate juice in elderly individuals and this activity was probably exerted by polyphenols present in the plant. Hamoud *et al.* (2014) showed an improvement of oxidative status in individuals with hypercholesterolemia after consumption of pomegranate

extract pills during statin therapy. A study by Kanlayavattanakul *et al.* (2020) demonstrated the antioxidant activity of phenolic-enriched pomegranate peel extract *in vitro*.

3.3. Effects on the reproductive system

Previous studies showed that pomegranate juice consumption ameliorates symptoms and comorbidity of PCOS (e.g., levels of testosterone, metabolic syndrome parameters and cardiovascular risk factors) (Abedini *et al.*, 2021; Esmaeilinezhad *et al.*, 2019; Esmaeilinezhad *et al.*, 2020). Chen and colleagues (2012) found that oral intake of pomegranate juice can prevent placental diseases. Another study demonstrated that pomegranate extract is useful in the treatment of idiopathic central precocious puberty (ICPP) together with gonadotropin-releasing hormone (GnRH) analog therapy (Liu and Tang, 2017).

3.4. Anticollitis activity

Kamali and colleagues (2015) showed that oral intake of pomegranate peels aqueous extract can improve clinical response in patients with ulcerative colitis.

3.5. Anticancer activity

Previous studies demonstrated that consumption of pomegranate juice and extracts can ameliorate clinical outcomes in prostate cancer patients (Paller *et al.*, 2013; Pantuck *et al.*, 2006). Another study found that this activity can be exerted by polyphenol metabolites (i.e., dimethyl ellagic acid and urolithin glucuronides) (González-Sarriás *et al.*, 2010). González-Sarriás and colleagues (2018) showed that oral intake of pomegranate extracts has a beneficial effect in patients with colorectal cancer by decreasing endotoxemia. Other two studies found that pomegranate extracts can regulate microRNAs and gene expression in colorectal cancer tissues (Nuñez-Sánchez *et al.*, 2015; Nuñez-Sánchez *et al.*, 2017). A preliminary study showed that oral

intake of pomegranate juice can be effective on the prevention of breast cancer by decreasing serum sex hormone levels (Kapoor *et al.*, 2015).

3.6. Cardiovascular effects

Previous studies demonstrated that oral consumption of pomegranate juice lowers triglycerides and blood pressure and improves high-density lipoprotein cholesterol (HDL-C) (Barati Boldaji *et al.*, 2020; Shema-Didi *et al.*, 2014) and atherosclerosis (Shema-Didi *et al.*, 2012) in patients undergoing hemodialysis. Wu and colleagues (2015) showed that pomegranate polyphenol extract is able to decrease blood pressure in hemodialysis patients, while Jafari *et al.* (2020) found that consumption of pomegranate peel extract and vitamin E can improve endothelial function in these patients. A previous study demonstrated that oral intake of concentrated pomegranate juice can lead to a reduction of total and low-density lipoprotein cholesterol (LDL-C) in diabetic hyperlipidemia (Esmailzadeh *et al.*, 2004). Other two studies found that oral intake of pomegranate juice decreases blood pressure in diabetic patients (Sohrab *et al.*, 2019) and in individuals with metabolic syndrome (Moazzen and Alizadeh, 2017). Mirmiran *et al.* (2010) demonstrated the beneficial activity of pomegranate seed oil on serum lipids in individuals with hyperlipidaemia. Another study found that oral intake of pomegranate extract pills has anti-atherogenic activity in subjects with hypercholesterolemia undergoing statin therapy (Hamoud *et al.*, 2014). Mathew and colleagues (2012) demonstrated that individuals who consumed a drink with ellagitannin-rich pomegranate extract displayed inhibition of postprandial improvement in systolic blood pressure after eating a high fat meal. A previous study showed the cardiovascular protective effect of urolithin present in pomegranate extract in subjects with obesity or overweight (González-Sarriás *et al.*, 2017). Hosseini and colleagues (2016) demonstrated the beneficial effects of pomegranate extract on cardiovascular system in individuals with overweight or obesity. Lynn and colleagues (2012) found that pomegranate

juice has a beneficial effect on blood pressure and Razani and colleagues (2017) showed that pomegranate juice has a therapeutic effect in ischemic heart disease. Another study demonstrated that oral consumption of pomegranate juice exerts health benefits on myocardial ischemia in individuals with ischemic coronary heart disease (Sumner *et al.*, 2005). Abedini and colleagues (2021) showed that pomegranate juice can prevent cardiovascular diseases, lowering triglycerides and blood pressure and raising HDL-C in PCOS patients. A study by Esmaeilinezhad *et al.* (2020) found that consumption of synbiotic pomegranate juice lowers blood pressure, total cholesterol and LDL-C, while improves HDL-C in individuals with PCOS.

3.7. Antidiabetic activity

Previous studies showed the beneficial effects of oral intake of pomegranate juice in diabetic patients, improving cardiovascular parameters (Sohrab *et al.*, 2019), glucose control (Banihani *et al.*, 2014), inflammatory (Sohrab *et al.*, 2018) and oxidative status (Rosenblat *et al.*, 2006; Sohrab *et al.*, 2017). Kerimi and colleagues (2017) demonstrated that pomegranate juice consumption can lower blood glucose levels after a bread meal through α -amylase inhibition by punicalagin and polyphenol metabolites, such as urolithins, can regulate glucose metabolism about 3-6 hours after the meal. A previous study by Hosseini *et al.* (2016) found that pomegranate extract reduces blood levels of insulin and glucose in individuals with overweight or obesity. Another study showed that pomegranate seed oil can ameliorate diabetic parameters in individuals with obesity and type 2 diabetes mellitus (T2DM) (Khajebishak *et al.*, 2019). Esmaeilinezhad and colleagues (2019) demonstrated that individuals with PCOS who consumed synbiotic pomegranate juice showed improved glycemic control. A study by Banihani *et al.* (2020) found that oral intake of pomegranate juice exerts beneficial effects in diabetic patients, lowering cortisol levels.

3.8. Effects on metabolic syndrome and obesity

Previous studies showed that pomegranate juice consumption ameliorates metabolic syndrome (Kojadinovic *et al.*, 2017; Moazzen and Alizadeh, 2017). Other two studies found that pomegranate juice (González-Ortiz *et al.*, 2011) or extract (Hosseini *et al.*, 2016) has beneficial effects in overweight or obese individuals. Esmaeilinezhad and colleagues (2019) showed reduced weight, waist circumference and body mass index (BMI) in women with PCOS drinking synbiotic pomegranate juice.

3.9. Antiparasitic activity

A study by El-Sherbini *et al.* (2010) demonstrated the antiparasitic activity of pomegranate extract against *Trichomonas vaginalis* *in vitro* and *in vivo*. Another study showed the beneficial effects of pomegranate extract against *Cryptosporidium parvum* in calves (Weyl-Feinstein *et al.*, 2014).

3.10. Antiarthritic activity

Previous studies found that pomegranate juice or extract can be beneficial for OA (Ghoochani *et al.*, 2016) and RA (Balbir-Gurman *et al.*, 2011; Ghavipour *et al.*, 2017) by improving the oxidative status.

3.11. Effects on skin health

Previous studies showed that oral intake of pomegranate juice, extract and extract rich in ellagic acid can protect the skin from ultraviolet (UV) radiation (Henning *et al.*, 2019; Kasai *et al.*, 2006). Kanlayavattanakul and colleagues (2020) demonstrated that phenolic-enriched pomegranate peel extract has beneficial effects against skin hyperpigmentation *in vitro* through enhanced antioxidant activity.

4. Discussion

In this review, we conducted a literature search to find the therapeutic effects of oral intake of pomegranate. Overall, we show 11 health benefits of this plant, including those on the nervous system, oxidative status, colitis, cancer, the cardiovascular system, diabetes, parasitic infections, arthritis, metabolic syndrome and obesity, the reproductive system and skin health.

Our results show that the most commonly reported therapeutic effect is antioxidant activity, which is described in 20 previous research studies. The beneficial effects of pomegranate on the cardiovascular system is also well reported in the scientific literature and 18 studies showed this plant medicinal property. The antidiabetic activity of pomegranate was examined in 10 studies (Table 1). Diabetes is a risk factor for cardiovascular diseases (Leon and Maddox, 2015) and previous research studies found that oxidative stress is involved in these conditions (Kattoor *et al.*, 2017; Maritim *et al.*, 2003; Sugamura and Keaney, 2011). In this review, we show that oral intake of pomegranate can ameliorate diabetes (Rosenblat *et al.*, 2006; Sohrab *et al.*, 2017) and cardiovascular parameters (Barati Boldaji *et al.*, 2020; Hamoud *et al.*, 2014; Shema-Didi *et al.*, 2012; Shema-Didi *et al.*, 2014) by improving the oxidative status. These therapeutic effects may be mediated by pomegranate phenolic compounds and metabolites (Chen *et al.*, 2012; González-Sarriás *et al.*, 2017; Gouda *et al.*, 2016; Guo *et al.*, 2008; Heber *et al.*, 2007; Kanlayavattanakul *et al.*, 2020; Kerimi *et al.*, 2017; Mathew *et al.*, 2012; Wu *et al.*, 2015). Most of the research studies focused on the medicinal properties of pomegranate juice instead of this plant extracts.

Anticancer activity of pomegranate is found in 7 research studies and this effect may be attributed to pomegranate polyphenol metabolites (González-Sarriás *et al.*, 2010) (Table 1). Previous research has focused on the activity of pomegranate against prostate (González-Sarriás

et al., 2010; Paller *et al.*, 2013; Pantuck *et al.*, 2006), colorectal (González-Sarrias *et al.*, 2018; Nuñez-Sánchez *et al.*, 2015; Nuñez-Sánchez *et al.*, 2017) and breast (Kapoor *et al.*, 2015) cancers. The health benefits of pomegranate on the reproductive system and the beneficial effects of this plant on obesity and metabolic syndrome are reported in 5 studies (Table 1). In this review, we show that the therapeutic effects of pomegranate on the reproductive system (Chen *et al.*, 2012; Esmaeilinezhad *et al.*, 2019; Esmaeilinezhad *et al.*, 2020) and obesity or overweight (Heber *et al.*, 2007; Hosseini *et al.*, 2016) can be mediated by improved oxidative status. Polyphenols may exert the beneficial activity on the reproductive system (Chen *et al.*, 2012) and overweight (Heber *et al.*, 2007).

Only few studies reported the therapeutic effects of pomegranate consumption on the nervous system, arthritis and skin health (3 studies), colitis (1 study) and parasitic infections (2 studies) (Table 1). The antiarthritic activity is mediated by the antioxidant effects of pomegranate (Balbir-Gurman *et al.*, 2011; Ghavipour *et al.*, 2017; Ghoochani *et al.*, 2016) and phenolic compounds and metabolites, which are present in this plant, may be beneficial for skin health (Henning *et al.*, 2019; Kanlayavattanakul *et al.*, 2020; Kasai *et al.*, 2006).

Future research is required to define the potential health benefits of pomegranate consumption and the phytochemicals involved in these activities. Limitations of this review are the following: most of the research studies utilise small sample sizes, only published articles are included and personal selection criteria are used.

5. Conclusion

This review describes the main medicinal properties of pomegranate consumption previously reported in the scientific literature. We show 11 health benefits of this plant, which include therapeutic effects on the cardiovascular system, oxidative status, diabetes, the nervous

system, colitis, cancer, metabolic syndrome and obesity, parasitic infections, arthritis, the reproductive system and skin health. The most commonly reported effects of oral intake of pomegranate are antioxidant, cardiovascular and antidiabetic activities and polyphenols present in this plant may exert the beneficial effects on human health. Future studies are needed to clarify the medicinal properties of pomegranate and the mechanisms underlying these activities.

Abbreviations

BMI: body mass index

GnRH: gonadotropin-releasing hormone

HDL-C: high-density lipoprotein cholesterol

ICPP: idiopathic central precocious puberty

IUGR: intrauterine growth restriction

LDL-C: low-density lipoprotein cholesterol

OA: osteoarthritis

PCOS: polycystic ovary syndrome

RA: rheumatoid arthritis

T2DM: type 2 diabetes mellitus

TAC: total antioxidant capacity

UV: ultraviolet

Statements and Declarations

Acknowledgements

We thank Maurizio Carturan and Lidia Novelli for useful discussions and support.

Funding

No funding was received for conducting this study.

Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

ADN, FG, FP and PZ contributed to the study conception and design. Literature search was performed by ADN. The first draft of the manuscript was written by ADN and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Reference list

- Abedini M, Ghasemi-Tehrani H, Tarrahi MJ, Amani R (2021) The effect of concentrated pomegranate juice consumption on risk factors of cardiovascular diseases in women with polycystic ovary syndrome: a randomized controlled trial. *Phytother Res* 35(1):442-451.
- Balbir-Gurman A, Fuhrman B, Braun-Moscovici Y, Markovits D, Aviram M (2011) Consumption of pomegranate decreases serum oxidative stress and reduces disease activity in patients with active rheumatoid arthritis: a pilot study. *Isr Med Assoc J* 13(8):474-479.
- Banihani SA, Makahleh SM, El-Akawi ZJ (2020) Short-term effect of fresh pomegranate juice on serum cortisol and thyroxine in patients with type 2 diabetes. *Curr Mol Med* 20(5):355-360.
- Banihani SA, Makahleh SM, El-Akawi Z, Al-Fashtaki RA, Khabour OF, Gharibeh MY, Saadah NA, Al-Hashimi FH, Al-Khasieb NJ (2014) Fresh pomegranate juice ameliorates insulin resistance, enhances β -cell function, and decreases fasting serum glucose in type 2 diabetic patients. *Nutr Res* 34(10):862-867.
- Barati Boldaji R, Akhlaghi M, Sagheb MM, Esmaeilinezhad Z (2020) Pomegranate juice improves cardiometabolic risk factors, biomarkers of oxidative stress and inflammation in hemodialysis patients: a randomized crossover trial. *J Sci Food Agric* 100(2):846-854.
- Bar-Ya'akov I, Tian L, Amir R, Holland D (2019) Primary metabolites, anthocyanins, and hydrolyzable tannins in the pomegranate fruit. *Front Plant Sci* 10:620.
- Bellone JA, Murray JR, Jorge P, Fogel TG, Kim M, Wallace DR, Hartman RE (2019) Pomegranate supplementation improves cognitive and functional recovery following ischemic stroke: a randomized trial. *Nutr Neurosci* 22(10):738-743.

- Chen B, Tuuli MG, Longtine MS, Shin JS, Lawrence R, Inder T, Michael Nelson D (2012) Pomegranate juice and punicalagin attenuate oxidative stress and apoptosis in human placenta and in human placental trophoblasts. *Am J Physiol Endocrinol Metab* 302(9):E1142-E1152.

- El-Sherbini GM, Ibrahim KM, El Sherbiny ET, Abdel-Hady NM, Morsy TA (2010) Efficacy of *Punica granatum* extract on in-vitro and in-vivo control of *Trichomonas vaginalis*. *J Egypt Soc Parasitol* 40(1):229-244.

- Esmaeilnezhad Z, Babajafari S, Sohrabi Z, Eskandari MH, Amooee S, Barati-Boldaji R (2019) Effect of synbiotic pomegranate juice on glycemic, sex hormone profile and anthropometric indices in PCOS: a randomized, triple blind, controlled trial. *Nutr Metab Cardiovasc Dis* 29(2):201-208.

- Esmaeilnezhad Z, Barati-Boldaji R, Brett NR, de Zepetnek JOT, Bellissimo N, Babajafari S, Sohrabi Z (2020) The effect of synbiotics pomegranate juice on cardiovascular risk factors in PCOS patients: a randomized, triple-blinded, controlled trial. *J Endocrinol Invest* 43(4):539-548.

- Esmailzadeh A, Tahbaz F, Gaieni I, Alavi-Majd H, Azadbakht L (2004) Concentrated pomegranate juice improves lipid profiles in diabetic patients with hyperlipidemia. *J Med Food* 7(3):305-308.

- Ghavipour M, Sotoudeh G, Tavakoli E, Mowla K, Hasanzadeh J, Mazloom Z (2017) Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in Rheumatoid Arthritis patients. *Eur J Clin Nutr* 71(1):92-96.

- Ghoochani N, Karandish M, Mowla K, Haghighizadeh MH, Jalali MT (2016) The effect of pomegranate juice on clinical signs, matrix metalloproteinases and antioxidant status in patients with knee osteoarthritis. *J Sci Food Agric* 96(13):4377-4381.

- González-Ortiz M, Martínez-Abundis E, Espinel-Bermúdez MC, Pérez-Rubio KG (2011) Effect of pomegranate juice on insulin secretion and sensitivity in patients with obesity. *Ann Nutr Metab* 58(3):220-223.

- González-Sarriás A, García-Villalba R, Romo-Vaquero M, Alasalvar C, Örem A, Zafrilla P, Tomás-Barberán FA, Selma MV, Espín JC (2017) Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: A randomized clinical trial. *Mol Nutr Food Res* 61(5).

- González-Sarriás A, Giménez-Bastida JA, García-Conesa MT, Gómez-Sánchez MB, García-Talavera NV, Gil-Izquierdo A, Sánchez-Alvarez C, Fontana-Compiano LO, Morga-Egea JP, Pastor-Quirante FA, Martínez-Díaz F, Tomás-Barberán FA, Espín JC (2010) Occurrence of urolithins, gut microbiota ellagic acid metabolites and proliferation markers expression response in the human prostate gland upon consumption of walnuts and pomegranate juice. *Mol Nutr Food Res* 54(3):311-322.

- González-Sarriás A, Núñez-Sánchez MA, Ávila-Gálvez MA, Monedero-Saiz T, Rodríguez-Gil FJ, Martínez-Díaz F, Selma M, Espín JC (2018) Consumption of pomegranate decreases plasma lipopolysaccharide-binding protein levels, a marker of metabolic endotoxemia, in patients with newly diagnosed colorectal cancer: a randomized controlled clinical trial. *Food Funct* 9(5):2617-2622.

- Gouda M, Moustafa A, Hussein L, Hamza M (2016) Three week dietary intervention using apricots, pomegranate juice or/and fermented sour sobya and impact on biomarkers of antioxidative activity, oxidative stress and erythrocytic glutathione transferase activity among adults. *Nutr J* 15(1):52.

- Grieve M (1931) *A Modern Herbal*. Dover Publications, New York.

- Guo C, Wei J, Yang J, Xu J, Pang W, Jiang Y (2008) Pomegranate juice is potentially better than apple juice in improving antioxidant function in elderly subjects. *Nutr Res* 28(2):72-77.

- Hamoud S, Hayek T, Volkova N, Attias J, Moscoviz D, Rosenblat M, Aviram M (2014) Pomegranate extract (POMx) decreases the atherogenicity of serum and of human monocyte-derived macrophages (HMDM) in simvastatin-treated hypercholesterolemic patients: a double-blinded, placebo-controlled, randomized, prospective pilot study. *Atherosclerosis* 232(1):204-210.

- Heber D, Seeram NP, Wyatt H, Henning SM, Zhang Y, Ogden LG, Dreher M, Hill JO (2007) Safety and antioxidant activity of a pomegranate ellagitannin-enriched polyphenol dietary supplement in overweight individuals with increased waist size. *J Agric Food Chem* 55(24):10050-10054.

- Henning SM, Yang J, Lee RP, Huang J, Hsu M, Thames G, Gilbuena I, Long J, Xu Y, Park EH, Tseng CH, Kim J, Heber D, Li Z (2019) Pomegranate juice and extract consumption increases the resistance to UVB-induced erythema and changes the skin microbiome in healthy women: a randomized controlled trial. *Sci Rep* 9(1):14528.

- Hosseini B, Saedisomeolia A, Wood LG, Yaseri M, Tavasoli S (2016) Effects of pomegranate extract supplementation on inflammation in overweight and obese individuals: a randomized controlled clinical trial. *Complement Ther Clin Pract* 22:44-50.

- Jafari T, Fallah AA, Reyhanian A, Sarmast E (2020) Effects of pomegranate peel extract and vitamin E on the inflammatory status and endothelial function in hemodialysis patients: a randomized controlled clinical trial. *Food Funct* 11(9):7987-7993.

- Jurenka JS (2008) Therapeutic applications of pomegranate (*Punica granatum L.*): a review. *Altern Med Rev* 13(2):128-144.

- Kamali M, Tavakoli H, Khodadoost M, Daghighzadeh H, Kamalinejad M, Gachkar L, Mansourian M, Adibi P (2015) Efficacy of the *Punica granatum* peels aqueous extract for symptom management in ulcerative colitis patients. A randomized, placebo-controlled, clinical trial. *Complement Ther Clin Pract* 21(3):141-146.

- Kandylis P, Kokkinomagoulos E (2020) Food applications and potential health benefits of pomegranate and its derivatives. *Foods* 9(2):122.

- Kanlayavattanakul M, Chongnativisit W, Chaikul P, Lourith N (2020) Phenolic-rich pomegranate peel extract: *in vitro*, cellular, and *in vivo* activities for skin hyperpigmentation treatment. *Planta Med* 86(11):749-759.

- Kapoor R, Ronnenberg A, Puleo E, Chatterton RT Jr, Dorgan JF, Seeram NP, Sturgeon SR (2015) Effects of Pomegranate Juice on Hormonal Biomarkers of Breast Cancer Risk. *Nutr Cancer* 67(7):1113-1119.

- Kasai K, Yoshimura M, Koga T, Arii M, Kawasaki S (2006) Effects of oral administration of ellagic acid-rich pomegranate extract on ultraviolet-induced pigmentation in the human skin. *J Nutr Sci Vitaminol* 52(5):383-388.

- Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL (2017) Oxidative Stress in Atherosclerosis. *Curr Atheroscler Rep* 19(11):42.

- Kerimi A, Nyambe-Silavwe H, Gauer JS, Tomás-Barberán FA, Williamson G (2017) Pomegranate juice, but not an extract, confers a lower glycemic response on a high-glycemic

index food: randomized, crossover, controlled trials in healthy subjects. *Am J Clin Nutr* 106(6):1384-1393.

- Khajebishak Y, Payahoo L, Alivand M, Hamishehkar H, Mobasser M, Ebrahimzadeh V, Alipour M, Alipour B (2019) Effect of pomegranate seed oil supplementation on the GLUT-4 gene expression and glycemic control in obese people with type 2 diabetes: A randomized controlled clinical trial. *J Cell Physiol* 234(11):19621-19628.
- Kojadinovic MI, Arsic AC, Debeljak-Martacic JD, Konic-Ristic AI, Kardum ND, Popovic TB, Glibetic MD (2017) Consumption of pomegranate juice decreases blood lipid peroxidation and levels of arachidonic acid in women with metabolic syndrome. *J Sci Food Agric* 97(6):1798-1804.
- Leon BM, Maddox TM (2015) Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 6(13):1246-1258.
- Levin GM (2006) Pomegranate. Third Millennium Pubns
- Liu J, Tang J (2017) Effects of pomegranate extract in supplementing gonadotropin-releasing hormone therapy on idiopathic central precocious puberty in Chinese girls: a randomized, placebo-controlled, double-blind clinical trial. *Food Funct* 8(2):695-700.
- Longtin R (2003) The Pomegranate: Nature's Power Fruit? *J Natl Cancer Inst* 95(5):346-348.
- Lynn A, Hamadeh H, Leung WC, Russell JM, Barker ME (2012) Effects of pomegranate juice supplementation on pulse wave velocity and blood pressure in healthy young and middle-aged men and women. *Plant Foods Hum Nutr* 67(3):309-314.

- Magangana TP, Makunga NP, Fawole OA, Opara UL (2020) Processing factors affecting the phytochemical and nutritional properties of pomegranate (*Punica granatum* L.) peel waste: a review. *Molecules* 25(20):4690.

- Maritim AC, Sanders RA, Watkins JB 3rd (2003) Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Mol Toxicol* 17(1):24-38.

- Mathew AS, Capel-Williams GM, Berry SE, Hall WL (2012) Acute effects of pomegranate extract on postprandial lipaemia, vascular function and blood pressure. *Plant Foods Hum Nutr* 67(4):351-357.

- Matthews LG, Smyser CD, Cherkerzian S, Alexopoulos D, Kenley J, Tuuli MG, Nelson DM, Inder TE (2019) Maternal pomegranate juice intake and brain structure and function in infants with intrauterine growth restriction: A randomized controlled pilot study. *PLoS One* 14(8):e0219596.

- Mazani M, Fard AS, Baghi AN, Nemati A, Mogadam RA (2014) Effect of pomegranate juice supplementation on matrix metalloproteinases 2 and 9 following exhaustive exercise in young healthy males. *J Pak Med Assoc* 64(7):785-790.

- Mirmiran P, Fazeli MR, Asghari G, Shafiee A, Azizi F (2010) Effect of pomegranate seed oil on hyperlipidaemic subjects: a double-blind placebo-controlled clinical trial. *Br J Nutr* 104(3):402-406.

- Moazzen H, Alizadeh M (2017) Effects of Pomegranate Juice on Cardiovascular Risk Factors in Patients with Metabolic Syndrome: a Double-Blinded, Randomized Crossover Controlled Trial. *Plant Foods Hum Nutr* 72(2):126-133.

- Nuñez-Sánchez MA, Dávalos A, González-Sarrias A, Casas-Agustench P, Visioli F, Monedero-Saiz T, García-Talavera NV, Gómez-Sánchez MB, Sánchez-Álvarez C, García-Albert AM, Rodríguez-Gil FJ, Ruiz-Marín M, Pastor-Quirante FA, Martínez-Díaz F, Tomás-Barberán FA, García-Conesa MT, Espín JC (2015) MicroRNAs expression in normal and malignant colon tissues as biomarkers of colorectal cancer and in response to pomegranate extracts consumption: Critical issues to discern between modulatory effects and potential artefacts. *Mol Nutr Food Res* 59(10):1973-1986.

- Nuñez-Sánchez MA, González-Sarrias A, García-Villalba R, Monedero-Saiz T, García-Talavera NV, Gómez-Sánchez MB, Sánchez-Álvarez C, García-Albert AM, Rodríguez-Gil FJ, Ruiz-Marín M, Pastor-Quirante FA, Martínez-Díaz F, Tomás-Barberán FA, Espín JC, García-Conesa MT (2017) Gene expression changes in colon tissues from colorectal cancer patients following the intake of an ellagitannin-containing pomegranate extract: a randomized clinical trial. *J Nutr Biochem* 42:126-133.

- Paller CJ, Ye X, Wozniak PJ, Gillespie BK, Sieber PR, Greengold RH, Stockton BR, Hertzman BL, Efros MD, Roper RP, Liker HR, Carducci MA (2013) A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer. *Prostate Cancer Prostatic Dis* 16(1):50-55.

- Pantuck AJ, Leppert JT, Zomorodian N, Aronson W, Hong J, Barnard RJ, Seeram N, Liker H, Wang H, Elashoff R, Heber D, Aviram M, Ignarro L, Belldegrun A (2006) Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res* 12(13):4018-4026.

- Razani Z, Dastani M, Kazerani HR (2017) Cardioprotective effects of pomegranate (*Punica granatum*) juice in patients with ischemic heart disease. *Phytother Res* 31(11):1731-1738.

- Rosenblat M, Hayek T, Aviram M (2006) Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. *Atherosclerosis* 187(2):363-371.
- Shabbir MA, Khan MR, Saeed M, Pasha I, Khalil AA, Siraj N (2017) Punicic acid: A striking health substance to combat metabolic syndromes in humans. *Lipids Health Dis* 16(1):99.
- Shema-Didi L, Kristal B, Ore L, Shapiro G, Geron R, Sela S (2013) Pomegranate juice intake attenuates the increase in oxidative stress induced by intravenous iron during hemodialysis. *Nutr Res* 33(6):442-446.
- Shema-Didi L, Kristal B, Sela S, Geron R, Ore L (2014) Does Pomegranate intake attenuate cardiovascular risk factors in hemodialysis patients? *Nutr J* 13:18.
- Shema-Didi L, Sela S, Ore L, Shapiro G, Geron R, Moshe G, Kristal B (2012) One year of pomegranate juice intake decreases oxidative stress, inflammation, and incidence of infections in hemodialysis patients: a randomized placebo-controlled trial. *Free Radic Biol Med* 53(2):297-304.
- Siddarth P, Li Z, Miller KJ, Ercoli LM, Merrill DA, Henning SM, Heber D, Small GW (2020) Randomized placebo-controlled study of the memory effects of pomegranate juice in middle-aged and older adults. *Am J Clin Nutr* 111(1):170-177.
- Sohrab G, Ebrahimof S, Sotoudeh G, Neyestani TR, Angoorani P, Hedayati M, Siasi F (2017) Effects of pomegranate juice consumption on oxidative stress in patients with type 2 diabetes: a single-blind, randomized clinical trial. *Int J Food Sci Nutr* 68(2):249-255.
- Sohrab G, Nasrollahzadeh J, Tohidi M, Zand H, Nikpayam O (2018) Pomegranate juice increases sirtuin1 protein in peripheral blood mononuclear cell from patients with type 2

diabetes: a randomized placebo controlled clinical trial. *Metab Syndr Relat Disord* 16(8):446-451.

- Sohrab G, Roshan H, Ebrahimof S, Nikpayam O, Sotoudeh G, Siasi F (2019) Effects of pomegranate juice consumption on blood pressure and lipid profile in patients with type 2 diabetes: a single-blind randomized clinical trial. *Clin Nutr ESPEN* 29:30-35.
- Sreekumar S, Sithul H, Muraleedharan P, Azeez JM, Sreeharshan S (2014) Pomegranate fruit as a rich source of biologically active compounds. *Biomed Res Int* 2014:686921.
- Sugamura K, Keaney JF Jr (2011) Reactive oxygen species in cardiovascular disease. *Free Radic Biol Med* 51(5):978-992.
- Sumner MD, Elliott-Eller M, Weidner G, Daubenmier JJ, Chew MH, Marlin R, Raisin CJ, Ornish D (2005) Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. *Am J Cardiol* 96(6):810-814.
- Urbaniak A, Basta P, Ast K, Wołoszyn A, Kuriańska-Wołoszyn J, Latour E, Skarpańska-Stejnborn A (2018) The impact of supplementation with pomegranate fruit (*Punica granatum* L.) juice on selected antioxidant parameters and markers of iron metabolism in rowers. *J Int Soc Sports Nutr* 15(1):35.
- Viuda-Martos M, Fernández-López J, Pérez-Álvarez J (2010) Pomegranate and its many functional components as related to human health: a review. *Compr Rev Food Sci Food Saf* 9:635-654.
- Zarfeshany A, Asgary S, Javanmard SH (2014) Potent health effects of pomegranate. *Adv Biomed Res* 3:100.

- Weyl-Feinstein S, Markovics A, Eitam H, Orlov A, Yishay M, Agmon R, Miron J, Izhaki I, Shabtay A (2014) *Short communication: effect of pomegranate-residue supplement on *Cryptosporidium parvum* oocyst shedding in neonatal calves.* J Dairy Sci 97(9):5800-5805.
- Wu PT, Fitschen PJ, Kistler BM, Jeong JH, Chung HR, Aviram M, Phillips SA, Fernhall B, Wilund KR (2015) Effects of Pomegranate Extract Supplementation on Cardiovascular Risk Factors and Physical Function in Hemodialysis Patients. J Med Food 18(9):941-949.

FIGURE LEGENDS

Fig. 1 The pomegranate. A botanical representation of pomegranate ("*Punica granatum*" by Adriana Morgante Giornetti)

Fig. 2 Punicic acid. 2D structure image of punicic acid. Retrieved from <https://pubchem.ncbi.nlm.nih.gov/compound/5281126#section=2D-Structure>

Fig. 3 Ellagic acid. 2D structure image of ellagic acid. Retrieved from <https://pubchem.ncbi.nlm.nih.gov/compound/5281855#section=2D-Structure>

Therapeutic effects of pomegranate	N° of research studies	References
Neuroprotective activity	3	Bellone <i>et al.</i> , 2019; Matthews <i>et al.</i> , 2019; Siddarth <i>et al.</i> , 2020
Antioxidant activity	20	Balbir-Gurman <i>et al.</i> , 2011; Barati Boldaji <i>et al.</i> , 2020; Chen <i>et al.</i> , 2012; Esmailinezhad <i>et al.</i> , 2019; Esmailinezhad <i>et al.</i> , 2020; Ghavipour <i>et al.</i> , 2017; Ghoochani <i>et al.</i> , 2016; Gouda <i>et al.</i> , 2016; Guo <i>et al.</i> , 2008; Hamoud <i>et al.</i> , 2014; Heber <i>et al.</i> , 2007; Hosseini <i>et al.</i> , 2016; Kanlayavattanakul <i>et al.</i> , 2020; Mazani <i>et al.</i> , 2014; Rosenblat <i>et al.</i> , 2006; Shema-Didi <i>et al.</i> , 2013; Shema-Didi <i>et al.</i> , 2012; Sohrab <i>et al.</i> , 2017; Urbaniak <i>et al.</i> , 2018; Wu <i>et al.</i> , 2015
Effects on the reproductive system	5	Abedini <i>et al.</i> , 2021; Chen <i>et al.</i> , 2012; Esmailinezhad <i>et al.</i> , 2019; Esmailinezhad <i>et al.</i> , 2020; Liu and Tang, 2017
Anticolitis activity	1	Kamali <i>et al.</i> , 2015
Anticancer activity	7	González-Sarriás <i>et al.</i> , 2010; González-Sarriás <i>et al.</i> , 2018; Kapoor <i>et al.</i> , 2015; Nuñez-Sánchez <i>et al.</i> , 2015; Nuñez-Sánchez <i>et al.</i> , 2017; Paller <i>et al.</i> , 2013; Pantuck <i>et al.</i> , 2006
Cardiovascular effects	18	Abedini <i>et al.</i> , 2021; Barati Boldaji <i>et al.</i> , 2020; Esmailinezhad <i>et al.</i> , 2020; Esmailzadeh <i>et al.</i> , 2004; González-Sarriás <i>et al.</i> , 2017; Hamoud <i>et al.</i> , 2014; Hosseini <i>et al.</i> , 2016; Jafari <i>et al.</i> , 2020; Lynn <i>et al.</i> , 2012; Mathew <i>et al.</i> , 2012; Mirmiran <i>et al.</i> , 2010; Moazzen and Alizadeh, 2017; Razani <i>et al.</i> , 2017; Shema-Didi <i>et al.</i> , 2014; Shema-Didi <i>et al.</i> , 2012; Sohrab <i>et al.</i> , 2019; Sumner <i>et al.</i> , 2005; Wu <i>et al.</i> , 2015
Antidiabetic activity	10	Banihani <i>et al.</i> , 2020; Banihani <i>et al.</i> , 2014; Esmailinezhad <i>et al.</i> , 2019; Hosseini <i>et al.</i> , 2016; Kerimi <i>et al.</i> , 2017; Khajebishak <i>et al.</i> , 2019; Rosenblat <i>et al.</i> , 2006; Sohrab <i>et al.</i> , 2017; Sohrab <i>et al.</i> , 2018; Sohrab <i>et al.</i> , 2019
Effects on metabolic syndrome and obesity	5	Esmailinezhad <i>et al.</i> , 2019; González-Ortiz <i>et al.</i> , 2011; Hosseini <i>et al.</i> , 2016; Kojadinovic <i>et al.</i> , 2017; Moazzen and Alizadeh, 2017
Antiparasitic activity	2	El-Sherbini <i>et al.</i> , 2010; Weyl-Feinstein <i>et al.</i> , 2014
Antiarthritic activity	3	Balbir-Gurman <i>et al.</i> , 2011; Ghavipour <i>et al.</i> , 2017; Ghoochani <i>et al.</i> , 2016
Effects on skin health	3	Henning <i>et al.</i> , 2019; Kanlayavattanakul <i>et al.</i> , 2020; Kasai <i>et al.</i> , 2006

Table 1. Beneficial effects of pomegranate on human health. The therapeutic properties of pomegranate, number of research studies and references are reported in the table.

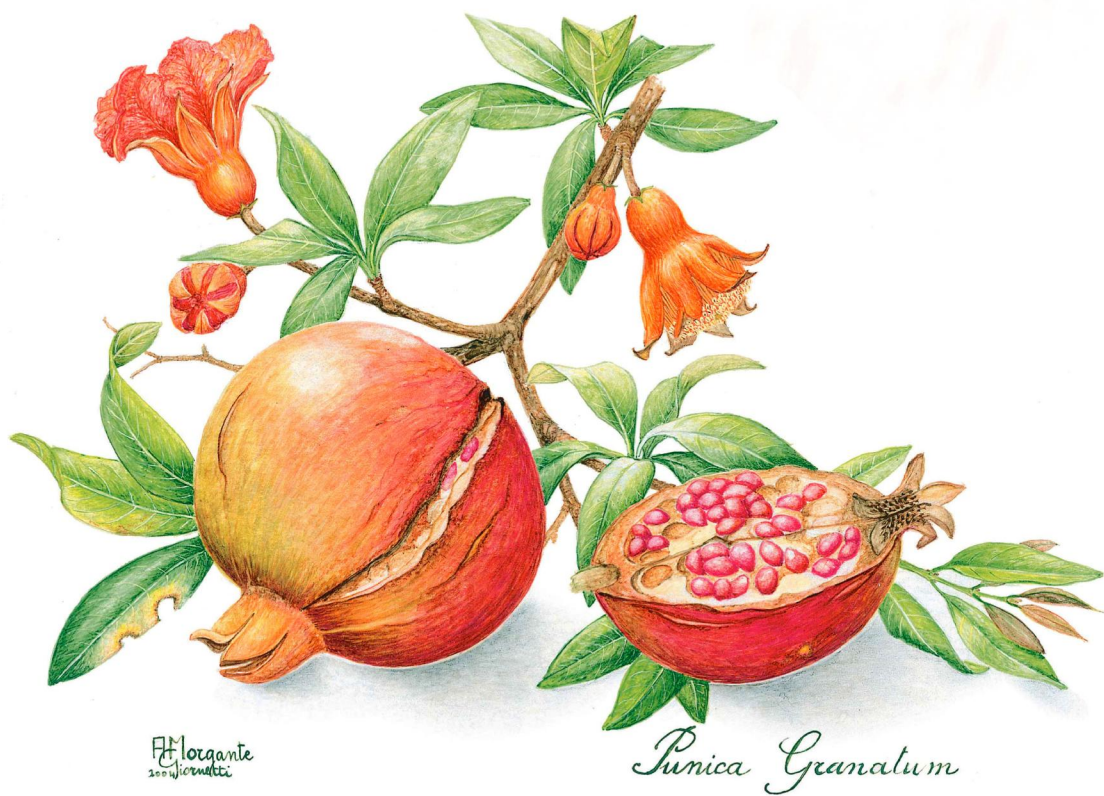


Fig. 1

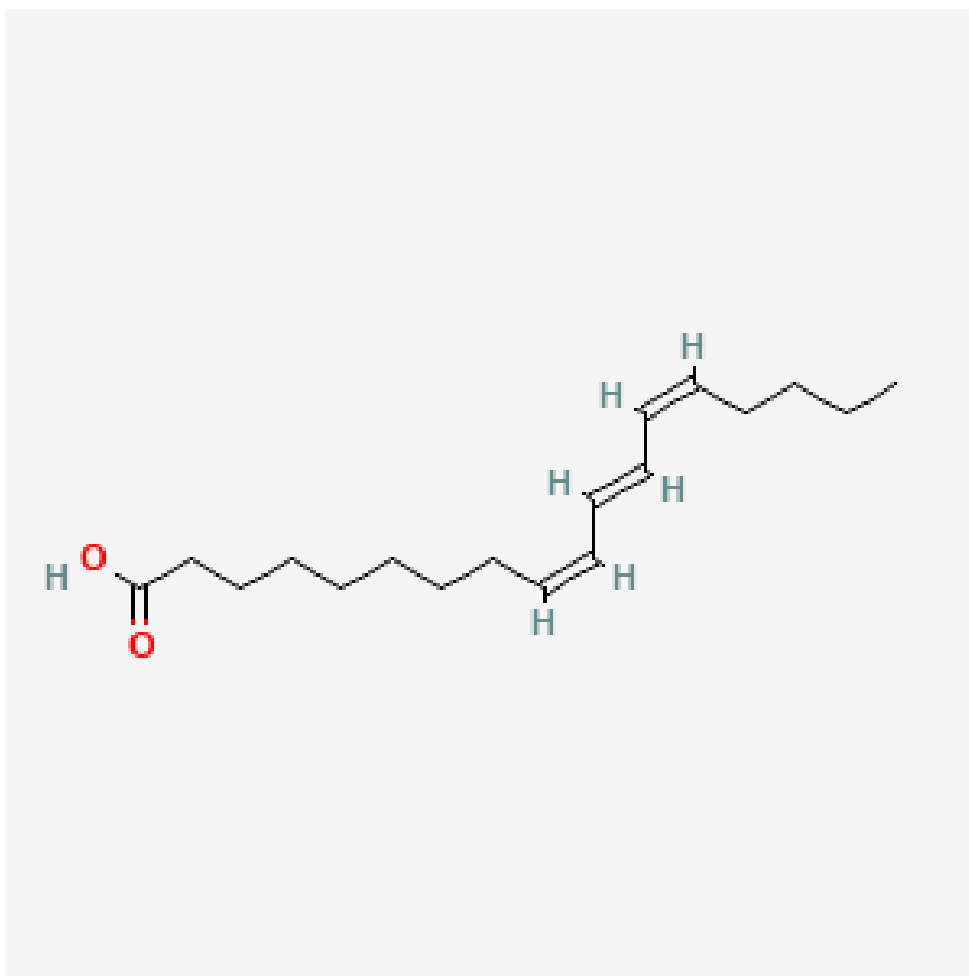


Fig. 2

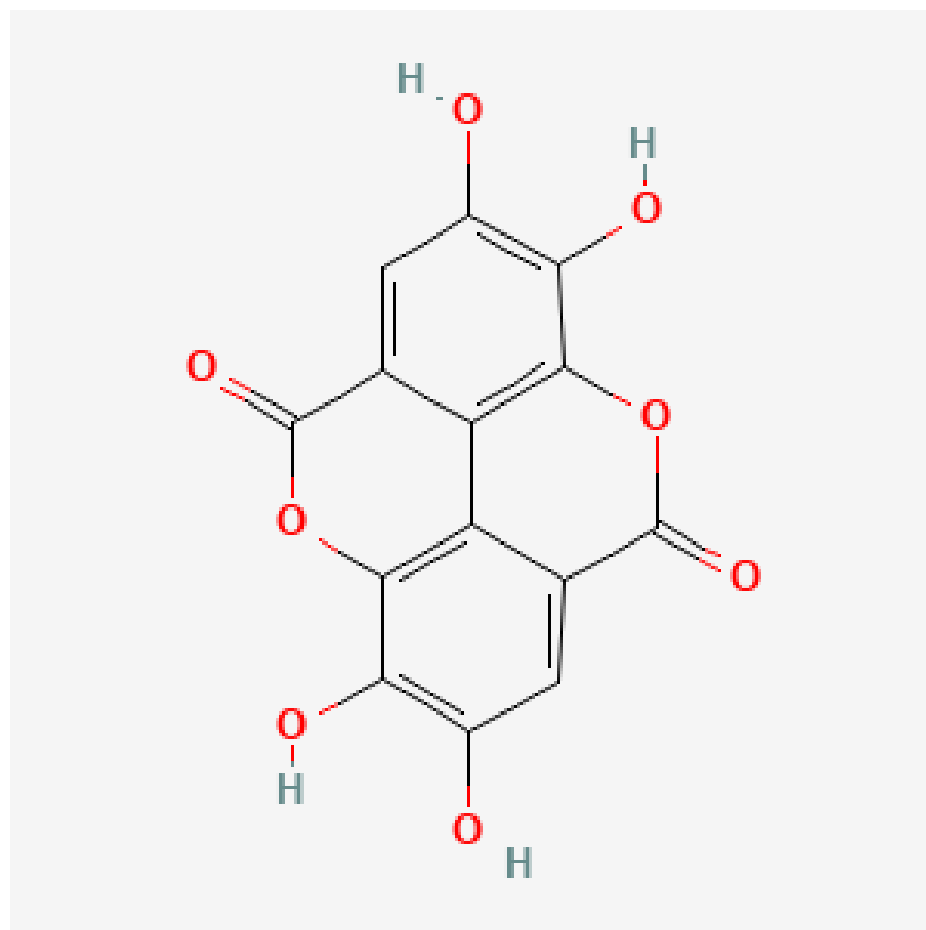


Fig. 3