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THE BENEFICIAL EFFECTS OF POMEGRANATE (*PUNICA GRANATUM* L.) CONSUMPTION ON HUMAN HEALTH: A REVIEW

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SUMMARY

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. The purpose of this review is to describe the health benefits of pomegranate, which are reported in the scientific literature. We performed a literature search, using the PubMed database. We utilized 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 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 beneficial properties of pomegranate may be exerted by polyphenols found in the plant. This review describes the health benefits of oral intake of pomegranate, which are mentioned in the scientific literature. 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 health properties. Future research is needed to define the beneficial effects of oral intake of this plant and the phytochemical compounds implicated in these activities.

Key words

Pomegranate; health benefits; antioxidant; cardiovascular; antidiabetic.

Impact statement

The consumption of pomegranate (*Punica granatum* L.) exerts beneficial effects on human health, such as cardiovascular, antidiabetic and antioxidant 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; LCAI: Lichtiger colitis activity index; LDL-C: low-density lipoprotein cholesterol; MED: minimal erythema dose; NF-kB: nuclear factor kappa B; OA: osteo-arthritis; PCOS: polycystic ovary syndrome; RA: rheumatoid arthritis; SIRT1: sirtuin1; T2DM: type 2 diabetes mellitus; TAC: total antioxidant capacity; UV: ultraviolet.

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) (1,2). "*Punica*" comes from the Latin words "*Punicum malum*", which mean "the Carthaginian apple". The Latin word "*granatum*" means "seeded" (3). *P. granatum* belongs to the Myrtales order and is considered a member of the family Lythraceae or Punicaceae (4). The plant can reach minimum and maximum heights of 1 and 10 meters, respectively, and can live up to 300 years (5). 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 color changes from green to yellow to red. The edible seeds and juice are enclosed in arils, which are located inside the fruit (3, 5- 7) (**figure 1**).

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 (8). Various phytochemicals are present in different parts of the plant and are considered responsible for its therapeutic effects, which are known since antiquity (9). Phytoestrogens and punicic acid are contained in seeds (7, 10) (**figure 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 (**figure 3**). Alkaloids are mainly found in roots and bark (8,11).

The pomegranate is consumed mainly as fruit, fresh juice, concentrated syrup, jelly, sauce, jam, tea infusion and plant extracts (*e.g.*, capsules and tablets) (7). 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 health properties of this plant and its use for preventing and treating different conditions.

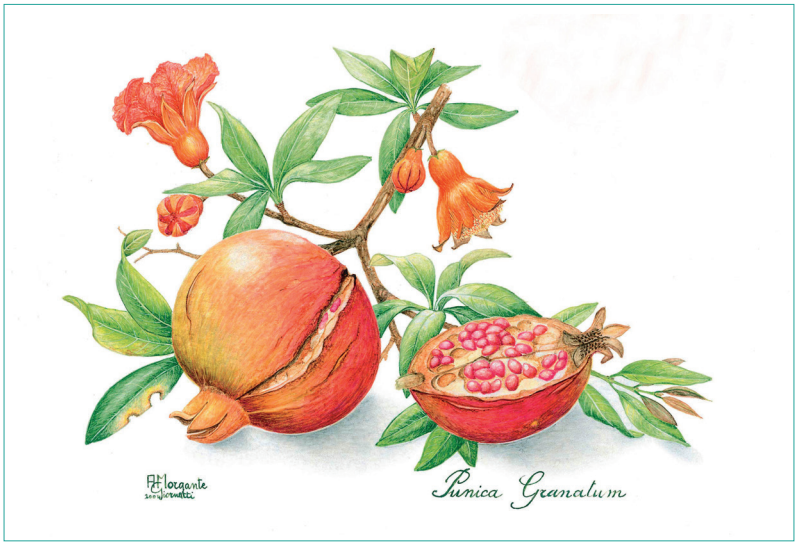

Figure 1. The pomegranate. A botanical representation of pomegranate ('*Punica granatum*' by Adriana Morgante Giornetti).

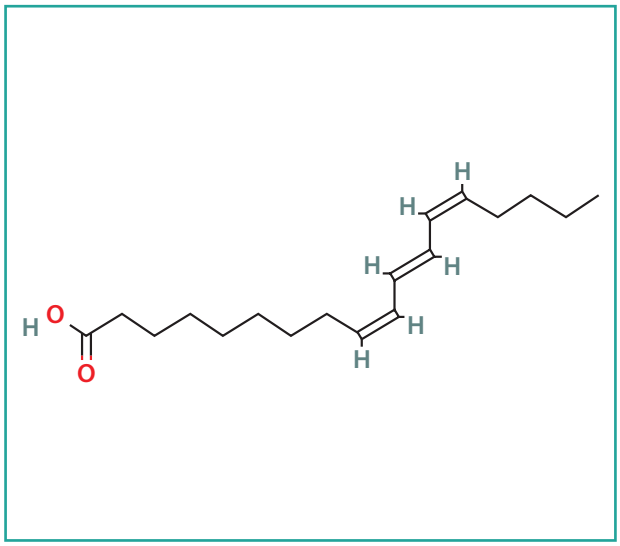

Figure 2. Punicic acid. 2D structure image of punicic acid. Retrieved from: https://pubchem.ncbi.nlm.nih.gov/compound/5281126#section=2D-Structure.

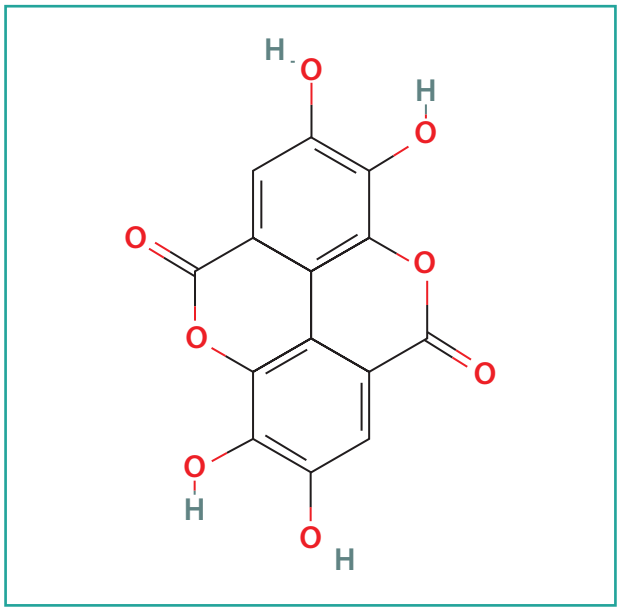

Figure 3. Ellagic acid. 2D structure image of ellagic acid. Retrieved from: https://pubchem.ncbi.nlm.nih.gov/compound/5281855#section=2D-Structure.

METHODS

We used the PubMed database (www.ncbi.nlm.nih.gov/pubmed) to find previous research studies, which described the beneficial 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.

RESULTS

Overall, we found 125 research studies, carrying out the literature search, and we selected 55 articles, which were suitable for defining the beneficial properties of pomegranate consumption. We describe 11 health 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 I**).

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

Therapeutic effects of pomegranate	N° of research studies	References	
Neuroprotective activity	3	Bellone *et al.*, 2019; Matthews *et al.*, 2019; Siddarth *et al.*, 2020	

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

Neuroprotective activity

A study by Siddarth *et al.* (12) showed that daily consumption of pomegranate juice over a period of 1 year can exert beneficial effects on visual memory in a sample of 200 aging individuals. Another study found that maternal intake of pomegranate juice exhibits neuroprotective effect in a cohort of 55 newborns with intrauterine growth restriction (IUGR) (13). Bellone and colleagues (14) showed that pomegranate polyphenol supplements enhance functional and cognitive outcomes, examining 16 stroke rehabilitation patients.

Antioxidant activity

A previous study by Urbaniak *et al.* (15) found that daily oral intake of pomegranate juice increases total antioxidant capacity (TAC)

in 19 athletes (*i.e.*, rowers). Mazani and colleagues (16) 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 12 human placenta *in vivo* and *in vitro* (17). Other studies demonstrated that consumption of probiotic pomegranate juice improves antioxidant activity in women with polycystic ovary syndrome (PCOS) (18, 19). A study by Heber *et al.* (20) found that oral consumption of ellagitannin-rich pomegranate extract exerts antioxidant effects in a cohort of 22 overweight individuals. Another study found that oral intake of pomegranate extract reduces oxidative stress in overweight or obese individuals (21). Gouda and colleagues (22) showed improved antioxidant activity in human plasma and urine after daily consumption of polyphenol-rich pomegranate juice in a sample of 35 healthy individuals. Other two studies showed the antioxidant activity of pomegranate juice in diabetic individuals (23, 24). Ghoochani and colleagues (25) found the antioxidant activity of pomegranate juice in a cohort of 38 patients with osteoarthritis (OA), while other two studies demonstrated that consumption of pomegranate extract has antioxidant activity in samples of six (26) and 55 (27) patients with rheumatoid arthritis (RA). Previous studies showed that drinking pomegranate juice three times per week improved the oxidative status, testing 41 (28) and 101 (29) individuals undergoing hemodialysis. A research work by Shema-Didi and colleagues (30) studied 27 patients and found an improvement in oxidative status during a single dialysis session. Another study demonstrated that pomegranate polyphenol extract has beneficial effects on oxidative stress in a cohort of 27 hemodialysis patients (31). Guo and colleagues (32) found increased antioxidant activity after daily oral intake of pomegranate juice in elderly individuals and this activity was probably exerted by polyphenols contained in the plant. Hamoud *et al.* (33) showed an improvement of oxidative status in individuals with hypercholesterolemia after consumption of pomegranate extract or placebo pills during statin therapy. A study by Kanlayavattanakul *et al.* (34) demonstrated the antioxidant activity of phenolic-enriched pomegranate peel extract *in vitro*.

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) (18, 19, 35). Chen and colleagues (17) 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, examining a cohort of 210 patients (36).

Anticolitis activity

Kamali and colleagues (37) showed that oral intake of pomegranate peels aqueous extract can improve clinical response in patients with ulcerative colitis. In this study, the Lichtiger colitis activity index (LCAI) was used to evaluate symptoms in a sample of 62 individuals aged 18-65 years. Patients were given pomegranate extract or placebo for four weeks. This study is characterized by a small sample size and is not informative about the mechanisms through which this plant has anti-ulcerative colitis effect but represents the first experimental evidence that pomegranate can exert this effect in humans. Other research works should confirm these findings.

Anticancer activity

Previous studies demonstrated that consumption of pomegranate juice and extracts can ameliorate clinical outcomes in prostate cancer, examining samples of 92 (38) and 42 (39) patients. Another study found that this activity can be exerted by polyphenol metabolites

(*i.e.*, dimethyl ellagic acid and urolithin glucuronides) (40). González-Sarrías and colleagues (41) showed that oral intake of pomegranate extracts has a beneficial effect in a cohort of 45 patients with colorectal cancer by decreasing endotoxemia. Other two studies found that pomegranate extracts can regulate microRNAs and gene expression in colorectal cancer tissues (42, 43). 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 (44).

Cardiovascular effects

Previous studies demonstrated that oral consumption of pomegranate juice lowers triglycerides and blood pressure and improves high-density lipoprotein cholesterol (HDL-C) (28, 45) and atherosclerosis (29) in patients undergoing hemodialysis. Wu and colleagues (31) showed that pomegranate polyphenol extract is able to decrease blood pressure in hemodialysis patients, while Jafari *et al.* (46) 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 (47). Other two research works found that oral intake of pomegranate juice decreases blood pressure, studying 60 diabetic patients (48) and 30 individuals with metabolic syndrome (49). Mirmiran *et al.* (50) demonstrated the beneficial activity of pomegranate seed oil on serum lipids in a sample of 45 individuals with hyperlipidemia. Another study found that oral intake of pomegranate extract pills has anti-atherogenic activity in subjects with hypercholesterolemia undergoing statin therapy (33). Mathew and colleagues (51) 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, testing a cohort of 19 healthy males. A previous study showed the cardiovascular protective effect of urolithin present in pomegranate extract in a sample of 49 subjects with obesity or overweight (52). Hosseini and colleagues (21) demonstrated the beneficial effects of pomegranate extract on cardiovascular system in individuals with overweight or obesity. Lynn and colleagues (53) found that pomegranate juice has a beneficial effect on blood pressure and Razani and colleagues (54) 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 a sample of 45 individuals with ischemic coronary heart disease (55). Abedini and colleagues (35) showed that pomegranate juice can prevent cardiovascular diseases, lowering triglycerides and blood pressure and raising HDL-C in a cohort of 42 PCOS patients. A study by Esmaeilinezhad *et al.* (19) found that consumption of synbiotic pomegranate juice lowers blood pressure, total cholesterol and LDL-C, while improves HDL-C in a sample of 92 individuals with PCOS.

Antidiabetic activity

Previous studies showed the beneficial effects of oral intake of pomegranate juice in diabetic patients. Sohrab and colleagues (48) found that consumption of pomegranate juice improves cardiovascular parameters in a cohort of 60 diabetic patients, lowering diastolic and systolic blood pressure. A study by Banihani *et al.* (56) evaluated the effect of pomegranate juice consumption on glucose control in a sample of 85 diabetic patients and found decreased fasting serum glucose and insulin resistance and improved pancreatic β-cell function. Sohrab and colleagues (57) showed improvement of the inflammatory status (*i.e.*, nuclear factor kappa B (NF-kB) and sirtuin1 (SIRT1) levels) in diabetic individuals, who were given pomegranate juice. Other two research works found an improvement of oxidative status in diabetic patients (23, 24). Kerimi and

colleagues (58) demonstrated in a sample of 16 healthy individuals that pomegranate juice consumption can lower blood glucose levels after a bread meal through α-amilase 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.* (21) 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 a cohort of 52 individuals with obesity and type 2 diabetes mellitus (T2DM) (59). Esmaeilinezhad and colleagues (18) demonstrated that individuals with PCOS who consumed synbiotic pomegranate juice showed improved glycemic control, testing 92 patients. A study by Banihani *et al.* (60) found that oral intake of pomegranate juice exerts beneficial effects in a sample of 89 diabetic patients, lowering cortisol levels.

Effects on metabolic syndrome and obesity

Previous studies showed that pomegranate juice consumption ameliorates metabolic syndrome, examining samples of 23 (61) and 30 (49) individuals. Other two studies found that pomegranate juice (62) or extract (21) has beneficial effects in overweight or obese individuals. González-Ortiz and colleagues (62) studied a sample of 20 obese participants. Esmaeilinezhad and colleagues (18) showed reduced weight, waist circumference and body mass index (BMI) in women with PCOS drinking synbiotic pomegranate juice.

Antiparasitic activity

A study by El-Sherbini *et al.* (63) 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 (64). These works provide experimental evidence of the antiparasitic effect of this plant in animals, humans and *in vitro*. However, other research studies are required, due to small sample sizes and the need of data replication of these findings. The mechanisms through which pomegranate extracts exert antiparasitic activity should be explained.

Antiarthritic activity

Previous studies found that pomegranate juice or extract can be beneficial for OA (25) and RA (26, 27) by improving the oxidative status. Balbir-Gurman and colleagues (26) demonstrated the effects of this plant extract in a small cohort of six postmenopausal females with RA, evaluating clinical symptoms and serum oxidative status. The study by Ghavipour *et al.* (27) evaluated the effect of pomegranate extract in a sample of 55 patients with RA and found an improvement in clinical symptoms and blood inflammatory and oxidative stress parameters. Ghoochani and colleagues (25) studied the health benefits of pomegranate juice in a cohort of 38 OA patients. They demonstrated that this plant could ameliorate clinical symptoms and serum oxidative stress and OA biomarkers.

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 (65, 66). Henning and colleagues (65) found that consumption of pomegranate juice and extract can improve minimal erythema dose (MED) and reduce melanin concentration in a sample of 74 healthy females. They also demonstrated that pomegranate consumption alters the skin microbiota, but they could not evaluate if the microbiota modification is involved in the UV protection. The study by Kasai *et al.* (66) demonstrated the beneficial effect of oral intake of ellagic acid-enriched pomegranate extract in a cohort of 37 healthy women through assessment of melanin, erythema and luminescence values. Kanlayavattanakul and colleagues (34) demonstrated that phenolic-enriched pomegranate

peel extract has beneficial effects against skin hyperpigmentation *in vitro* through enhanced antioxidant activity.

DISCUSSION

In this review, we conducted a literature search to find the health benefits of oral intake of pomegranate. Overall, we show 11 beneficial effects 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 health property 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 health benefit. The antidiabetic activity of pomegranate was examined in 10 studies (**table I**). Diabetes is a risk factor for cardiovascular diseases (67) and previous research studies found that oxidative stress is involved in these conditions (68, 69, 70). In this review, we show that oral intake of pomegranate can ameliorate diabetes (23, 24) and cardiovascular parameters (28, 29, 33, 45) by improving the oxidative status. These beneficial effects may be mediated by pomegranate phenolic compounds and metabolites (17, 20, 22, 31, 32, 34, 51, 52, 58). Most of the research studies focused on the beneficial properties of pomegranate juice instead of this plant extracts.

Anticancer activity of pomegranate is found in seven research studies and this effect may be attributed to pomegranate polyphenol metabolites (40) (**table I**). Previous research has focused on the activity of pomegranate against prostate (38-40), colorectal (41-43) and breast (44) 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 five studies (**table I**). In this review, we show that the effects of pomegranate on the reproductive system (17-19) and obesity or overweight (20, 21) can be mediated by improved oxidative status. Polyphenols may exert the beneficial activity on the reproductive system (17) and overweight (20).

Only few studies reported the beneficial effects of pomegranate consumption on the nervous system, arthritis, and skin health (three studies), colitis (one study) and parasitic infections (two studies) (**table I**). The antiarthritic activity is mediated by the antioxidant effects of pomegranate (25-27) and phenolic compounds and metabolites, which are present in this plant, may be beneficial for skin health (34, 65, 66).

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.

CONCLUSIONS

This review describes the main beneficial properties of pomegranate consumption previously reported in the scientific literature. We show 11 health benefits of this plant, which include positive 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 health properties 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 health benefits of pomegranate and the mechanisms underlying these activities, as we are still unsure of the potential impacts of this plant and its bioactive compounds on human health.

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ETHICS

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Conflict of interest
The authors declare that they have no conflict of interests.

Availability of data and material
All data and material are available upon request.

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.

Ethical approval
N/A.

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