Pomegranate Peel and Its Anticancer Activity: A Mechanism-Based Review

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Contents

Abstract

Cancer is one of the prominent death causing diseases around the globe. About 1 in 6 deaths is due to cancer and its related diseases. Cancer mortality can be reduced by early diagnosis and screening, implementing effective treatments.

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A precise cancer identification is vital for effective treatment, because each cancer type requires a definite treatment procedure, such as radiotherapy, surgery, and chemotherapy. The brisk expansion of herbal therapy and escalating ongoing clinical studies are becoming trendy and useful in the drug development against cancer. Pomegranate (*Punica granatum*) is a prehistoric fruit with illustrious dietary and remedial properties in alternative traditional systems of medicine. The current chapter is aiming to understand various model systems (in silico, in vitro, and in vivo), employed for studying its anti-cancerous properties and diverse molecular effects exhibited by the pomegranate peel and its phytoconstituents. It also highlights the importance of secondary metabolites of *P. granatum*, especially ellagitannins and their anticancer properties. Although there are enormous in vitro and preclinical data, human clinical trials are sorely lacking. The major focus is on up-to-date investigations into the outcomes of previously reported pomegranate peel components against a diverse type of cancers.

Keywords
Cancer · Ellagitannins · Molecular targets · *Punica granatum* · Pomegranate · Treatment

10.1 Introduction

Modern medicine and therapies offer cure for most ailments in today's world, but in some cases, they lead to numerous critical side effects, as seen in the case of cancer therapy (Yin et al. 2013). Nevertheless, much before the use of allopathic medicines, plant-based products were commonly used globally for improving health conditions. There are plenty of functional foods and herbs that are available today, and they possess phytocompounds, which play a vital role in curing a plethora of diseases like jaundice (Kamala et al. 2018), diabetes (Middha et al. 2014; 2019), inflammation (Prashanth Kumar et al. 2019), mouth ulcers, cancer, etc. (Lee et al. 2012). Despite the remarkable advances in diagnostics and therapeutics, cancer (malignancy) is branded to be the deadliest disease. The mortality associated with cancer can be reduced drastically by early diagnosis, intervention, and prevention measures. Epidemiological investigations have indicated that intake of natural products, such as vegetables and fruits, can reasonably decrease the risk of cancer incidence (Donaldson 2004; Syed et al. 2013). There is also a growing use of herbal medicine by cancer patients, due to their safety aspects and cost-effectiveness. Pomegranate (*Punica granatum*), which has been termed as a "Superfood" (Middha et al. 2013a), due to its multiple biological properties is one such plant that holds a great potential for treating cancers (Sharma et al. 2017).

Pomegranate is thought to have taken its root throughout the world, initially being cultivated in Iran, followed by the Himalayan regions of India and different microclimatic zones (Middha et al. 2016). It is a drought-resistant plant that has a long life span approximating up to 200 years with high and healthy fruit yield in the first 20 years (Zarfeshany et al. 2014). The flush, visual appearance, flavor, and

antioxidant competence of the fruit are known to be influenced by the climatic circumstances in which the plant exists. It is a spiny deciduous plant belonging to the plant family, Punicaceae (new classification Lythraceae), which also houses another species *Punica protopunica* (Socotran pomegranate). Punicaceae is placed under the subclass, Rosidae belonging to the order of Myrtales. Pomegranate has small slender leaves, heterostylous funnel-shaped red flowers and the fruit having 5–12 cm diameter with a hexagonal rounded figure amid an upright crown (Singh et al. 2018). The fruiting body can be separated majorly into three parts, namely, rind/husk/pericarp/peel/skin, aril, and the seeds, as shown in Fig. 10.1. It is a plant rich in nutrients and phytochemicals. Be it any part of the pomegranate, i.e., peel, juice, root, bark, flowers, leaves, or seeds, all of them possess potent therapeutic properties. It also targets a range of diseases, including cancer, diabetes, cardiovascular disorders, aging, male infertility, Alzheimer's disease, and Acquired Immune Deficiency Syndrome (AIDS) (Viuda-Martos et al. 2010; Middha et al. 2013a, b). The pomegranate fruit and the other nonedible parts are loaded with anthocyanidins, anthocyanins, flavanols, flavones, flavonones, phenolic acids, and tannins (punicalagin and punicalin). The pharmacological outcome of pomegranate extracts could be linked to their polyphenolic richness (Rummun et al. 2013). The whole genome data have further helped in elucidating genetics, evolution, and other interesting pharmacological effects of pomegranate (Qin et al. 2017).

Pomegranate peel, an affluent natural antioxidant and having varied chemical molecules, was accounted previously for its diverse pharmacological properties such as aging, Alzheimer's disease, cancer, cardiovascular disorders, diabetes, and infertility disorders (Middha et al. 2013a, b; Sun et al. 2016; Singh et al. 2018). This systemic chapter benefits the readers in understanding the usage of pomegranate peel as a natural and alternative medicine in cancer prevention, as it emphasizes the antiproliferative, antimetastatic, and anti-invasive role of pomegranate peel and summarizes its mechanism using an array of cancer cell lines (in vitro), preclinical and clinical models.

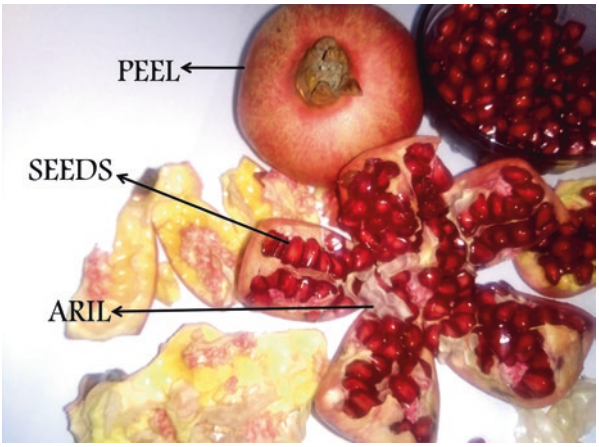

Fig. 10.1 Major parts of pomegranate

10.2 History and Cultural Significance of Pomegranate Peel

Pomegranate is one among the only two species of the kind in *Punica* genus belonging to the family Lythraceae (previously, Punicaceae) (Qin et al. 2017). The common name, *Punica*, is the feminized Latin term for Carthage (the capital town of the prehistoric Carthaginian society, Tunisia). It is originally derived from the Greek Phoinix referring to the Phoenician settlers around Carthage. The precise epithet, granatum, implies seedy or grainy. Prior to its rechristening by Linnaeus in the eighteenth century, the plant was identified as *Malum punicum*, the apple of Carthage (Stover and Mercure 2017). Another representation by few historians stated that the "Tree of Life" in the holy Bible was a pomegranate tree.

The Arabic or Semitic (rumman) and Biblical Hebrew (rimmon) names used for pomegranate mean "fruit of paradise" and has been known to be a symbol of love since ancient times. Pomegranate has been associated with fertility, abundance, immortality, invincibility, blessings, prosperity, posterity, and the endurance of marriage (Stover and Mercure 2017). The Greek physician Soranus documented five prescriptions for the seeds or rind of pomegranate to be used as oral contraceptives or vaginal (douche) suppositories (Foster and Johnson 2006). The contraceptive use of pomegranate seeds or rinds has also been elucidated by Hippocrates (468–377 BCE), Dioscorides (40–90 CE), and Ibn Sina (Avicenna, 980–1037 CE). Historically, pomegranate has been significant in numerous cultures for its food and medicinal uses, as well as for its spiritual and artistic symbolism. The Ebers Papyrus from Egypt (one of the oldest preserved medical documents, ca. 1500 BCE) prescribed it as a remedy for roundworm (Ebbell 1937). Dried fruit rind and pulp have been used commonly for upset stomachs and diarrhea, prepared as infusions (teas) or tinctures (alcoholic extractions) (Van-Wyk and Wink 2004).

Most parts of the pomegranate, including the leaves, fruits, flowers, rind, dried seeds and fresh seeds, trunk bark or root bark, fresh fruits, and preparations thereof (e.g., juice), have defined therapeutic applications in the traditional medicinal systems, such as Ayurveda, Siddha (Traditional Indian), gSo-ba Rig-pa (Traditional Bhutanese), Sowa-Rigpa (Traditional Tibetan), Traditional Chinese Medicine (TCM), Traditional Iranian Medicine, Unani (Perso-Arabic traditional medicine), and European Homeopathy. The fresh fruits and fruit juice are used widely as food, and the juice is also used as a rich source of polyphenols. Essential oils and extracts from different parts of the fruit, as well as isolates and derivatives, such as pomegranate fruit peel extract octenylsuccinate, seed oil hydroxyphenethyl esters, and sterols obtained from the seed oil are used as cosmetic ingredients (Van-Wyk and Wink 2004). In TCM, pomegranate husk/rind/peel (called shi liu pi) is utilized to cure dysentery, diarrhea, rectal prolapse, spermatorrhea, premature ejaculation, uterine bleeding, and vaginal discharge due to kidney instability, and to kill and expel parasites. It is also used topically for ringworm (Bensky 1993) and in combination with other herbs for the conditions mentioned above.

10.3 Characteristics of Pomegranate Peel

The peel is tough and leathery, about 2–5 inches in width, and its color ranges from yellow to deep pink/red. The peel makes almost 50% of the entire mass of the product (fruit) (Fawole et al. 2012). This part of the pomegranate is exceptionally rich in astringent properties and possesses many ethnomedical applications, due to the presence of numerous phytocompounds, but is usually disregarded as agricultural waste (Middha et al. 2013a).

10.3.1 Physicochemical Composition of Pomegranate Peel

The peel of pomegranate is said to be rich in lot of nutrients. The occurrence of total solid, total sugars, reducing sugars, proteins, crude fiber, fat content, and ash is shown to occur in the peels of pomegranate. Apart from these, it is rich in calcium, complex polysaccharides, minerals, nitrogen, magnesium, potassium, phosphorus, and sodium (Middha et al. 2013b).

10.3.2 Phytochemicals of Pomegranate Peel and their Medicinal Properties

Previous studies have shown that the peel is rich in tannins, flavonoids, alkaloids, and organic acids. Tannins, high-molecular-weight polyphenols, are organically and chemically divided into three divergent groups: condensed tannins (also called proanthocyanidins), hydrolyzable tannins or ellagitannins (ETs), and gallotannins (GTs). Pomegranate peel is found to be rich in hydrolyzable tannins, such as punicalin, punicalagin, and other tannins like pedunculagin, gallic acid, and casuarinin are predominantly present. Hence, it possesses superior antioxidative property. Isolariciresinol (10.5 mg/kg) is one of the predominant lignins present in the peel (Syed et al. 2013; Rahmani et al. 2017). Numerous flavonoids, such as catechin, epicatechin, epigallocatechin-3-gallate, flavan-3-ol, kaempferol (Al-Rawahi et al. 2014), kaempferol-3-O-glucoside, kaempferol-3-O-rhamnoglycoside (Akhtar et al. 2015; Moradian et al. 2017), luteolin, luteolin 7-O-glucoside, naringin, pelargonidin, prodelphindin, quercetin (Middha et al. 2013a, b), and rutin, are observed to be present in the peel, as reported from different experimental works (Wang et al. 2004). These phytochemicals attribute to the antibacterial, antioxidant, anti-inflammatory, antiviral, and antineoplastic effects of the peel. Also, there is the existence of gallic acid, gallagyldilacton, and granatin B, which provide anti-inflammatory activity to the peel (Satomi et al. 1993). A plethora of evidence suggests that the presence of these polyphenolics has rendered the peel with the property of anticarcinogenic activity. A total of 108 compounds (Table 10.1) have been reported to be present in the peel through various studies using High Performance Liquid Chromatography (HPLC) and Gas Chromatography–Mass Spectrometry (GC–MS) methods (Syed et al. 2013; Barathikannan et al. 2016; Middha et al. 2013a, b).

Table 10.1 Chemical constituents present in the pomegranate peel

S. no.	Name of the chemical constituent	Molecular formula	References
Polyphenols			
1	Caffeic acid	$C_9H_8O_4$	Viuda-Martos et al. (2010)
2	Valoneic acid dilactone	$C_{21}H_{10}O_{13}$	Jain et al. (2012, b)
3	4,4′-Di-O-methylellagic acid	$C_{16}H_{10}O_8$	Jain et al. (2012, b)
4	3-O-methylellagic acid	$C_{15}H_8O_8$	Jain et al. (2012, b)
5	Brevifolin carboxylic acid	$C_{13}H_8O_8$	Jain et al. (2012, b)
6	*p*-Coumaric acid/4-hydroxycinnamic acid	$C_9H_8O_3$	Viuda-Martos et al. (2010); Mushtaq et al. (2015)
7	Methylgallate	$C_8H_8O_5$	Mushtaq et al. (2015)
8	Caffeoylquinic acid/chlorogenic acid	$C_{16}H_{18}O_9$	Viuda-Martos et al. (2010)
9	Ellagic acid	$C_{14}H_6O_8$	Viuda-Martos et al. (2010); Middha et al. (2013b)
10	Gallic acid	$C_7H_6O_5$	Viuda-Martos et al. (2010); Middha et al. (2013b)
11	Vanillic acid	$C_8H_8O_4$	Mushtaq et al. (2015)
12	Syringic acid	$C_9H_{10}O_5$	Mushtaq et al. (2015)
13	Cinnamic acid	$C_9H_8O_2$	Viuda-Martos et al. (2010)
14	Ferulic acid	$C_{10}H_{10}O_4$	Mushtaq et al. (2015)
15	Sinapic acid	$C_{11}H_{12}O_5$	Mushtaq et al. (2015)
16	p-Coumaric acid glucuronide	–	Mushtaq et al. (2015)
17	Hydroxybenzoic acid	$C_7H_6O_3$	Viuda-Martos et al. (2010)
Tannins			
1	Punicalin	$C_{34}H_{22}O_{22}$	Viuda-Martos et al. (2010); Fischer et al. (2011)

(continued)

Table 10.1 (continued)

S. no.	Name of the chemical constituent	Molecular formula	References
2	Punicalagin	$C_{48}H_{28}O_{30}$	Zahin et al. (2010); Middha et al. (2013b); Y-q et al (2017)
3	Granatin A	$C_{34}H_{24}O_{22}$	Seeram et al. (2005)
4	Granatin B	$C_{41}H_{28}O_{27}$	Seeram et al. (2005)
5	Pedunculagin	$C_{34}H_{24}O_{22}$	Seeram et al. (2005)
6	Punicalin	$C_{34}H_{22}O_{22}$	Seeram et al. (2005)
7	Corilagin	$C_{27}H_{22}O_{18}$	Satomi et al. (1993)
8	Castalagin	$C_{41}H_{26}O_{26}$	Satomi et al. (1993)
9	2.3-(S)-Hexahydroxydiphenoyl (HHDP)-d-glucose	$C_{20}H_{18}O_{14}$	Satomi et al. (1993)
10	Gallagic acid	$C_{28}H_{14}O_{18}$	Satomi et al. (1993)
11	Casuarinin	$C_{41}H_{28}O_{26}$	Satomi et al. (1993)
12	*Caffeoylquinic acid or Chlorogenic acid*	$C_{16}H_{18}O_9$	Arnoni et al. (2015)
13	Tellimagrandin	$C_{41}H_{30}O_{26}$	Barathikannan et al. (2016)
14	Prodelphindin	$C_{30}H_{26}O_{13}$	Barathikannan et al. (2016)
Gallotannins			
1	*Digalloyl-hexoside/Glucogallin*	$C_{13}H_{16}O_{10}$	Fisher et al. (2011))
2	*Monogalloyl-hexoside/Glucogallin*	$C_{13}H_{16}O_{10}$	Fisher et al. (2011)
Flavonoids			
1	Cyanidin (anthocyanins)	$C_{15}H_{11}O_6^+$	Viuda-Martos et al. (2010)
2	Delphinidin (anthocyanins)	$C_{15}H_{11}ClO_7$	Viuda-Martos et al. (2010)
3	Pelargonidin-3-O-glucoside (anthocyanins)	$C_{21}H_{21}ClO_{10}$	Viuda-Martos et al. (2010)
4	Catechin	$C_{15}H_{14}O_6$	Wafa et al. (2017)
5	Gallocatechin	$C_{15}H_{14}O_7$	Wafa et al. (2017)
6	Procyanidin B	$C_{30}H_{26}O_{12}$	Wafa et al. (2017)

(continued)

Table 10.1 (continued)

S. no.	Name of the chemical constituent	Molecular formula	References
7	Myricetin	$C_{15}H_{10}O_8$	Wu and Tian. (2017)
8	Quercetin	$C_{15}H_{10}O_7$	Middha et al. (2013b)
9	Kaempferol (Flavonols)	$C_{15}H_{10}O_6$	Wafa et al. (2017)
10	Luteolin (flavone)	$C_{15}H_{10}O_6$	Wafa et al. (2017)
11	Apigenin (flavone)	$C_{15}H_{10}O_5$	Wu and Tian. (2017)
12	Rutin (O-glycosides)	$C_{27}H_{30}O_{16}$	Middha et al. (2013b)
14	Cyanidin-3-rutinoside (anthocyanins)	$C_{27}H_{31}O_{15}^+$	Wafa et al. (2017)
15	Cyanidin-3-pentoside (anthocyanins)		Wafa et al. (2017)
16	Cyanidin-3,5-diglucoside (anthocyanins)	$C_{27}H_{31}O_{16}^+$	Wafa et al. (2017)
17	Cyanidin-3-O-glucoside (anthocyanins)	$C_{21}H_{21}O_{11}^+$	Wafa et al. (2017)
18	Cyanidin 3-rutinoside (anthocyanins)	$C_{27}H_{31}O_{15}^+$	Wafa et al. (2017)
19	Delphinidin 3,5-diglucoside (anthocyanins)	$C_{27}H_{31}O_{17}^+$	Wafa et al. (2017)
20	Delphinidin 3-glucoside	$C_{21}H_{21}O_{12}^+$	Wafa et al. (2017)
21	Pelargonidin	$C_{15}H_{11}O_5^+$	Middha et al. (2013b)
22	Pelargonidin-3,5-diglucoside (anthocyanins)	$C_{27}H_{31}ClO_{15}$	Fisher et al. (2011)
23	Pelargonidin-3-glucoside	$C_{21}H_{21}O_{10}^+$	Fisher et al. (2011)
24	Delphinidin 3-glucoside (anthocyanins)	$C_{21}H_{21}O_{12}^+$	Fisher et al. (2011)
Alkaloid			
1	Pelletierine	$C_8H_{15}NO$	Barathikannan et al. (2016)
Tocopherols			
1	α-Tocopherol, γ-tocopherol, and δ-tocopherol/vitamin E	$C_{29}H_{50}O_2$	Elfalleh et al. (2011)
Terpene			
1	Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-,[1R-(1R*,4Z,9S*)]	$C_{15}H_{24}$	Barathikannan et al. (2016)
Unclassified category			
1	Heptadecane	$C_{17}H_{36}$	Barathikannan et al. (2016)

(continued)

Table 10.1 (continued)

S. no.	Name of the chemical constituent	Molecular formula	References
2	Triacotane	$C_{31}H_{64}$	Barathikannan et al. (2016)
3	Octadecane	$C_{18}H_{38}$	Barathikannan et al. (2016)
4	Squalene	$C_{30}H_{50}$	Barathikannan et al. (2016)
5	Eicosane	$C_{20}H_{42}$	Barathikannan et al. (2016)
6	5-Hydroxymethylfurfural (furan)	$C_6H_6O_3$	Barathikannan et al. (2016)
7	4-Mercaptophenol/4-Hydroxythiophenol	C_6H_6OS	Barathikannan et al. (2016)
8	Quinic acid	$C_7H_{12}O_6$	Barathikannan et al. (2016)
9	Heneicosane	$C_{21}H_{44}$	Barathikannan et al. (2016)
10	5-Hydroxymethylfurfural	–	Barathikannan et al. (2016)
11	4-Fluorobenzyl alcohol	–	Barathikannan et al. (2016)
12	Hexadecane, 1-iodo-Hexadecane Nonane	–	Barathikannan et al. (2016)
13	Z-8-Hexadecane, 9-Eicosene, (E)-n-Pentadecanol	–	Barathikannan et al. (2016)
14	Alpha-Copaene, alpha-Cubebene	–	Barathikannan et al. (2016)
15	Hexadecane, 2-Bromotetradecane	–	Barathikannan et al. (2016)
16	Heneicosane, 11-pentyl-Docosane, 11-butyl-Tridecane	–	Barathikannan et al. (2016)
17	Nonadecane, 9-methyl-Nonane, 5-butyl-Heptadecane	–	Barathikannan et al. (2016)
18	Z-8-hexadecane, Pentafluoropropionic acid, 4-hexadecyl ester	–	Barathikannan et al. (2016)
19	Nonadecane, 9-methyl, 7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione.	–	Barathikannan et al. (2016)
20	Pentadecanoic acid, 14-methyl aster, Hexadecanoic acid, methyl ester	–	Barathikannan et al. (2016)
21	Nonadecane, 9-methyl, Eicosane, Pentacosane	–	Barathikannan et al. (2016)
22	1-Heneicosyl formate, Cyclooctacosane, (Z)-9-Tricosen	–	Barathikannan et al. (2016)
23	Triacontane, 1-bromo-1-Chloroeicosane Heptadecane	–	Barathikannan et al. (2016)
24	Dodecane, 2,6,11-trimethyl-docosane, 7-hexyl-Tetracosane	–	Barathikannan et al. (2016)

(continued)

Table 10.1 (continued)

S. no.	Name of the chemical constituent	Molecular formula	References
25	Linoleic acid ethyl ester, n-Propyl 9,12-octadecadienoate, 9,12-octadecadienoic acid, ethyl ester	–	Barathikannan et al. (2016)
26	1-Nonadecene, 9-Trocosene, (Z)-Bacchotricuneatin	–	Barathikannan et al. (2016)
27	1-Nonadecene, 9-Trocosene, Z-5-Nonadecene	–	Barathikannan et al. (2016)
28	Heptadecane	–	Barathikannan et al. (2016)
29	6-Octen-1-ol, 3,7-dimethyl acetate Phytol, acetate 1,2–15, 16-Diepoxyhexadecane	–	Barathikannan et al. (2016)
30	3,5,7-Tricyclopropyl-5,6-dihydro-5-methyl-1,2 (4H)-diazepineOctanoic acid, but-3-yn-2-yl ester Ethisterone	–	Barathikannan et al. (2016)
31	3H-Cyclodeca[b]furan-2-one, 4,9-dihydroxy-6-methyl-3,10-dimethylene-3a,4,7,8,9,10,11,11a-octahydro-Bicyclo [10.1.0] trideca-4,8-diene-1 3-carboxamide,N-(3-chlorophenyl)-1H-2, 8a-Methanocyclopenta[a]cyclopropa[e] cyclodecen-11-one, 1a,2,5,5a,6,9,10,10a-octahydro-5,5a,6-trihydroxyl-1,4-bis(hydroxymethyl)-1,7,9-trimethyl [1S-(1.Alpha., 1a.Alpha., 2.Alpha., 5. Beta.,5a.Beta., 6.Beta., 8a.Aipha., 9. Alpha., 10a.Alpha.)]	–	Barathikannan et al. (2016)
32	Heptadecane, 3-methyl-Octadecane, Nonadecane	–	Barathikannan et al. (2016)
33	Octacosane, Tetracosane	–	Barathikannan et al. (2016)
34	Hexatriacontane, Octadecane, 1-iodo-Tetracontane	–	Barathikannan et al. (2016)
35	1-Hexacosene, 9-hexacosene, E-15-heptadecenal	–	Barathikannan et al. (2016)
36	CyclobarbitalTris(tert-butyldimethylsilyloxy)arsane, 1H-Indole-2-carboxylic acid, 6-(4-ethoxyphenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydro isopropyl ester	–	Barathikannan et al. (2016)
37	2,4-Cyclohexadien-1-one, 3,5-bis, 1-dimethylethyl-4-hydroxy-Tetrasiloxane, decamethyl-Benz[b]-1,4-oxazepine-4(5H)-thione, 2,3-dihydro-2,8-dimethyl	–	Barathikannan et al. (2016)
38	Anthracene, 9,10-dihydro-9,9,10-trimethyl-1H-Indole, 1-methyl-2-phenyl-Ethanone, 2-(2-benzothiazolylthio)-1-(3,5-dimethylpyralyl)	–	Barathikannan et al. (2016)

(continued)

Table 10.1 (continued)

S. no.	Name of the chemical constituent	Molecular formula	References
39	N-Methyl-1-adamantaneacetamide Arsenous acid, tris(trimethylsilyl)ester, Benzo[h]quinolone, 2,4-dimethyl	–	Barathikannan et al. (2016)
40	9,19-Cyclolanost-24-en-3-ol, Lanosterol, Lanost-7-en-3-one	–	Barathikannan et al. (2016)
42	Tirucallol, Lanosterol, D:B-Friedo-18, 19-secolup-19-ene, 10-epoxy	–	Barathikannan et al. (2016)
43	1,2-Bis(trimethylsilyl) benzene, 4-Dehydroxy-N-(4,5-methylenedioxy-2-nitrobenzylidene) tyramineBenzo[h] quinolone, 2,4-dimethyl	–	Barathikannan et al. (2016)
44	1H-Indole, 1-methyl-2-phenyl-Arsenous acid, tris(trimethylsilyl) ester, Cyclotrisiloxane, hexamethyl	–	Barathikannan et al. (2016)
45	Furan-2-carboxamide, N-(3-nitrophenyl)-1-propanone, 1-(2-furanyl)-4-pyrridinol	–	Barathikannan et al. (2016)
46	Benzene, 1,3-bis(1,1-dimethylethyl), benzene, 1,4-bis(1,1-dimethylethyl)	–	Barathikannan et al. (2016)
47	5-Hydroxymethylfurfural, 4-fluorobenzyl alcohol	–	Barathikannan et al. (2016)
48	5-methyl-2-phenylindozine (1H) Pyrrole-3-carboxylic acid, 5-[cyano(4-morpholinyl) methyl]-1-(methoxymethyl), methyl ester 2-(Acetoxymethyl)-3-(methoxycarbonyl) biphenylene	–	Barathikannan et al. (2016)

10.4 Anticancer Activity of Pomegranate Peel

The World Health Organization (WHO) and the American Cancer Society (ACS) reported that globally the second growing fatal disease is cancer, claiming approximately 9.6 million mortality in 2018. Around 1 in 6 demises worldwide is caused by malignancy and roughly 70% of these mortalities transpire in low- and middle-revenue nations. According to the ACS 2018 statistics in the United States (USA), an approximated 1,735,350 latest cancer cases in various hospitals/institutions and 609,640 cancer demises are witnessed (http://www.who.int/news-room/ fact-sheets/detail/cancer).

The currently available cancer treatments include radiotherapy, surgery, and systemic cures comprising cytotoxic chemotherapy, hormonal remedy, immunotherapy, and intentioned or targeted therapies such as hydrogels and magnetogels (Veloso et al. 2018). Although numerous therapies are available, all of them have their own side effects and some of them even create a financial burden on the patient. So, there is an urgent need for definitive preventive measures and complete cure for cancer, which will have lesser systemic toxicity as well as one that will not drill a

hole in the patient's pocket (Thomford et al. 2018). Recently, the advances in novel cancer remedies have become a major issue owing to the cells developing resistance to modern chemotherapy. Alternatively, in the present time, an herbal therapy is in focus owing to its less costs and toxicity. The current chapter attempts to summarize the literature available in PubMed and Google Scholar on the various model systems (in silico, in vitro, and in vivo) utilized to examine the anticancerous activities of peel and different molecular effects exhibited by the pomegranate peel (Table 10.2). A number of studies have centered on the anticancerous properties of pomegranate peel using in silico, in vitro, and in vivo model systems. The early scientific evidences majorly focused on the antidiarrheal activity of pomegranate peel and its genotoxicity studies. For the first time, Settheetham and Ishida (1995) reported that the administration of pomegranate aqueous extract encouraged DNA fragmentation during apoptosis in Raji and P3HR-1 cells. Though there was a huge gap until 2004, the later years have witnessed a drastic increase and interest in the anticancer and other pharmacological properties of pomegranate peel. This chapter also focuses on the demand for pomegranate peel and its derived compounds and their anticancer properties. Interestingly, the extracts of pomegranate peel have shown a selective inhibition against various types of cancer cells with no or less visible toxicity in normal cells.

10.4.1 Pomegranate Peel Against Breast Cancer

Breast cancer is a very commonly occurring cancer type in females around the world with an impact on more than 1.5 million women every year. It is also a reason for the massive number of cancer-related fatalities in women. A plethora of scientific evidence suggests that the consumption of phytochemicals-rich food can trim down the threat of cancer disease. Pomegranate peel extract (PPE), the biowaste material, is rich in polyphenols. Ricci et al. (2006) reported that the fruit juice has a higher polyphenolic content (0.063–0.0003 mg/g dry weight) than different varieties of the pomegranate peel (1.892–0.1070 mg/g dry weight) (Dikmen et al. 2011). In vitro and in vivo explorations have divulged that PPE, rich in polyphenols, act as potent antioxidants, which help in the inhibition of cell growth in cancer. Jeune et al. (2005) performed a study that demonstrated the in vitro anticancer effects of combining pomegranate extracts and genistein. They also proposed that the combination of both is more efficacious, as compared to single treatments in a time- and dose-dependent manner. They used lactate dehydrogenase, 3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium bioassays, acridine orange–ethidium bromide, and terminal deoxyribonucleotidyl transferase-mediated dUTP nick-end labeling to study the cytotoxic and growth inhibition effects of pomegranate extracts and genistein on MCF-7 cancer cells. Similar studies were also carried out by Dikmen et al. (2011) to demonstrate that the methanolic extract of pomegranate peel at varied concentrations (25, 50, 100, 200, and 300 μg/ml)

Table 10.2 Summary of molecular targets and anticancer potential of the pomegranate peel

Type of cancer	Model used (cells/animals)	Target pathway	References
Breast cancer	MDA-MB-231 cells	Decreases the gene expression of vimentin gene, zinc finger E-box-binding homeobox 1 (ZEB1), and β-catenin Increases the expression of E-cadherin Inhibits epithelial mesenchymal transition and metastasis	Bagheri et al. (2018)
	MCF-7, PC-3, and HepG-2	Solid lipid nanoparticles of pomegranate peel reduce the cell growth	Badawi et al. (2018)
	MCF-7 cancer cell line	Monodisperse platinum nanoparticles (Pt NPs) biosynthesized from pomegranate peel inhibit cell proliferation with a IC50 of 17.84 μg/ml after 48 h of incubation	Sahin et al. (2018)
	MCF-7 cell line	Silver nanoparticles of pomegranate peel inhibit the proliferation of cell at a dose of 12.85 μg/ml	Sahin et al. (2017)
	MCF-7 cell line	Downregulates the estrogen response element (ERE)-mediated transcription in breast cancer cells	Vini et al. (2016)
	MCF-7 cell line	Exhibits antiproliferative activity	Modaeinama et al. (2015)
	MCF-7 cell line	Increases the expression of Bax (pro-apoptotic gene) and reduces B-cell lymphoma 2 (Bcl-2) expression (anti-apoptotic gene) cell proliferation and induces apoptosis on MCF-7 cancer cells	Dikmen et al. (2011)
	Human breast MCF-7	Methanolic and acetone extract of pomegranate peel exhibits antiproliferative activity	Fazio et al. (2018)
	Human metastatic breast cancer cell line – MDA-MB-231	Upregulates the expression of intercellular adhesion molecule 1 (ICAM-1) Downregulates the expression of matrix metallopeptidase-9 (MMP-9), fibronectin, and vascular endothelial growth factor (VEGF)	Ahmadiankia et al. (2018)

(continued)

Table 10.2 (continued)

Type of cancer	Model used (cells/animals)	Target pathway	References
Colorectal cancer	Female dark Agouti rats (100–140 g, 6 weeks old)	Ameliorates 5-FU-induced intestinal mucositis	Chen et al. (2018)
	HT-29 CRC cell line	Induces intrinsic apoptosis with a decrease in mitochondrial potential, increases bcl-2-like protein 4 (BAX) to Bcl-2 ratio, and cleaves caspase-9 and caspase-3	
	Apc-mutated Pirc rats	Exhibits pro-apoptotic and anti-inflammatory action	Tortora et al. (2018)
	HT29 cells	Reduces cyclooxygenase-2 (COX-2) protein expression by 70% shows increase in caspase-3 (CASP-3) expression in cells	
Colon cancer	Colon (LoVo) cancer cell lines	Reduces the cell proliferation	Moreira et al. (2017)
	RKO: ATCC® CRL-2577™ cells	12.5 µg of silver nanoparticles from *Punica granatum* peel caused reduction in cell proliferation with viabilities of 56% and 61% on days 3 and 5, respectively.	Devanesan et al. (2018)
Prostate cancer	TRAMP-C1 DU145 and PC3 cells	Reduces mitochondrial transmembrane potential (Δym) Helps in the accumulation of reactive oxygen species (ROS) Induces apoptosis Impairs metastasis by downregulating matrix metalloproteinase-2/matrix metalloproteinase-9 (MMP-2/MMP-9) and upregulating tissue inhibitor of Metallopeptidase inhibitor 2 (TIMP2)	Deng et al. (2017)
	PC-3 cells	Exhibits antiproliferative activity	Modaeinama et al. (2015)
	LNCaP-AR and LAPC4 cells	Mediates nuclear factor κappa-light-chain-enhancer of activated B cells (NF-κB) blockade Reduction in S-phase fraction and accumulation of cells in the G1 phase	Retti et al. (2008)
	SCID mice implanted with LAPC4 prostate cancer LAPC4 xenograft model	Inhibits the growth of androgen-independent LAPC4 xenografts with an increase in Ki63 (proliferation marker) Enhances apoptosis Reduces phospho-IκBα levels	

(continued)

Table 10.2 (continued)

Type of cancer	Model used (cells/animals)	Target pathway	References
Cervical cancer	HeLa cells	Ellagic acid from peel inhibition of cervical cancer by promoting IGFBP7 expression Inhibits the protein kinase B/mammalian target of rapamycin (AKT/mTOR) signaling pathway by enhancing the expression level of insulin-like growth factor binding protein 7 (IGFBP7)	Guo et al. (2016)
Hepatocellular carcinoma	Male albino rats exposed to the hepatocarcinogen diethylnitrosamine (DENA)	Decreases the tumor size, liver index, and the anti-apoptotic protein Bcl-2 in liver Increases the amount of glutathione in liver Exhibits antimutagenic effect	El-Ashmawy et al. (2016)
	Hep-G2 cells	Cell cycle of HepG-2 arrested at the S-phase by inducing mitochondrial apoptotic pathway in a dose-dependent manner Increases Cyt-c 32 and the activity of Caspase-3/9 ROS levels increased Increases the ratio of Bax/Bcl-2 Increases protein expressions of P53	Song et al. (2016)
Urinary bladder cancer	Bladder cancer T24 cells	Ethyl acetate extract of pomegranate peel exhibits antiproliferative activity	Masci et al. (2016)
	EJ bladder cancer cells	Suppresses the EJ cell proliferation Promotes caspase-dependent apoptosis Decreases the expression of c-Jun and increases the expression of p53 The c-Myc and CD44 are the direct targets of MicroRNA-34a (miR-34a) in EJ cell apoptosis induced by the peel.	Zhou et al. (2015)
	Balb C nude mice	Decreases the tumor growth volume with no toxicity in the liver, spleen, and intestine of mice	
Ovarian cancer	SKOV3 cells	Inhibits increase in the uterine weight	Sreeja et al. (2012)
	Ovariectomized Swiss albino mice	Decreases cell proliferation in ovariectomized mice	
	SK-OV-3 cells	Exhibits antiproliferative activity	Deng et al. (2017)
Chronic myeloid leukemia	K562 cells	Promotes the growth inhibition of K562 cells, mainly via the G2/M phase arrest Upregulates caspases and cytochrome c Elevates the expression of p21 and p53	Asmaa et al. (2015)

(continued)

Table 10.2 (continued)

Type of cancer	Model used (cells/animals)	Target pathway	References
Lung cancer	A549 (lung nonsmall cell cancer)	Exhibits antiproliferative activity	Modaeinama et al. (2015)
Osteosarcoma	U-2 osteosarcoma (OS) cells	Induces the arrest of G2/M phase Induces apoptosis through the intrinsic mitochondrial pathway Inhibits the growth of cells in a dose-dependent manner Shows increase in the Bax/Bcl-2 ratio Decreases the mitochondrial membrane potential, release of cytochrome c, activation of caspase-9 and caspase-3, and cleavage of poly-(ADP-ribose)-polymerase (PARP)	Li et al. (2014)
Thyroid cancer	Human papillary thyroid cancer cell lines BCPAP (harboring BRAF V600E mutation) TPC-1 cell lines Nthy-ori 3–1 (human thyroid follicular epithelial cell line)	Inhibits proliferation and influences the morphology of thyroid cancer cells Induces cell apoptosis Induces the loss of mitochondrial transmembrane potential ($\Delta\Psi m$) and ROS generation Decreases the expression of MMP-9 and indicates the inhibition of thyroid cancer cell migration and invasion	Li et al. (2016)
	BALB/c Nude mice (5–6 weeks old)	Tumor volumes and weight significantly decreased Increases cleaved caspase-3 (CC-3)-positive cells And decreases Ki-67-positive cells No pathologic changes were observed in the heart, liver, spleen, lung, and kidney after the pomegranate peel treatment	
Skin cancer	Human epidermal keratinocytes and dermal fibroblasts	Stimulates type I procollagen synthesis and inhibits matrix metalloproteinase-1 (MMP-1; interstitial collagenase) production by dermal fibroblasts that promote the regeneration of dermis	(Aslam et al. 2006)

(continued)

Table 10.2 (continued)

Type of cancer	Model used (cells/animals)	Target pathway	References
Lung cancer, gastric cancer, prostate cancer, breast cancer, and liver cancer	In silico study	Quercetin, one of the chemical constituents, inhibits the following proteins/receptors: GTPase HRas, proto-oncogene tyrosine-kinase Src, tyrosine-protein kinase HCK, HSP 90-alpha, cell division protein kinase 2, basic fibroblast growth factor receptor 1, Cyclin A2, glycogen synthase kinase 3 beta, estradiol 17-beta-dehydrogenase 1, leukotriene A-4 hydrolase, lysozyme C, death-associated protein kinase 1, vitamin D3 receptor, apoptosis regulator BCL-X, proto-oncogene lymphocyte-specific protein tyrosine-protein kinase (LCK), serine/threonine-protein kinase polo-like kinase 1 gene (PLK1), Serine/threonine (Ser/thr) protein kinase, cell division protein kinase 9, casein kinase II subunit alpha, Cyclin-dependent kinase 6, proto-oncogene tyrosine-protein kinase receptor RET, androgen receptor, NAD(P)H dehydrogenase [quinone]	(Usha et al. 2015)

Note: *MDA-MB* M.D. Anderson-metastasis breast cancer, *MCF-7* Michigan cancer foundation-7, *PC-3* prostate cancer 3, *HepG-2* liver hepatocellular cells, *IC50* half-maximal inhibitory concentration, *HT-29* CRC human colorectal adenocarcinoma cell line, *Apc-Mutated* adenomatous polyposis coli, *PC3* human prostate cancer cell line, *LAPC4* los angeles prostate cancer-4, *SCID* severe combined immunodeficiency, *LNCaP* metastatic lesion of human prostatic adenocarcinoma

decreased cell proliferation and stimulated apoptosis in MCF-7 cancer cells. This was evident from the enhanced expression of pre-apoptotic gene Bax and decrease in the expression of anti-apoptotic gene Bcl-2. The effect of PPE was proportional to the dose and the incubation interval. Bcl-2/Bax plays a vital function in regulating caspase-dependent and caspase-independent apoptosis mediated by the mitochondrial pathway. The possible anticancer and apoptotic effects of pomegranate peel can be credited to ellagic acid, ellagic tannin, and gallic acid. The data gathered from both these studies aid to invent new chemotherapeutic and chemopreventive agents of pomegranate peel to treat breast cancer.

10.4.2 Pomegranate Peel Against Colorectal Cancer

Colorectal cancer (CRC) is the anomalous division of cells that occur in the colon or rectum or colorectum, also called the large intestine. As per the Cancer Statistics 2018 report, colorectal cancer is the third most familiar cancer to be detected equally

in both men and women in the United States. The WHO reports approximately 862,000 CRC deaths across the globe in 2018 (https://www.who.int/news-room/fact-sheets/detail/cancer). Siegel et al. (2016) reported that roughly 4.6% of man (1 in 22) and 4.2% of women (1 in 24) will be identified with CRC in their life span. Waly et al. (2012) observed an improvement in the redox status and decrease in preneoplastic lesions of the colonic cells in azoxymethane (AOM)-induced in vivo colon tumors treated with PPE. The proposition that PPE extracts might prevent colon cancer was based on in vitro studies that showed the high antioxidant properties of pomegranate peel. Increasing evidences have implicated that the augment in reactive oxygen species (ROS) is one of the causes of cell damage and cancer. In this context, Negi et al. (2003) used two strains of *Salmonella typhimurium* (*S. typhimurium)*, i.e., TA100 and TA1535, to test the efficacy of PPE extracts against sodium azide mutagenicity. The study revealed that strong antimutagenicity of soxhlet extracts of water, methanol, and ethyl acetate pomegranate peel at 2500 μg decreased mutagenicity in both strains of *Salmonella* species. The antioxidant and antimutagenic effects could be the result of the polyphenols, such as catechins, chlorogenic, caffeic, ellagic acid, and ferulic acids, present in the peel.

10.4.3 Pomegranate Peel Against Prostate Cancer

Prostate cancer (Pca) is accountable for the highest number of cancer cases reported in men. It accounts for every 1 in 5 new cancers diagnosed in men according to the American Cancer Society (Siegel et al. 2016). According to Cancer Statistics 2018 reports of the American Institute for Cancer Research, prostate cancer is the second most lethal cancer spotted in men with 1.3 million new cases in the United States (https://www.wcrf.org/dietandcancer/cancer-trends/prostate-cancer-statistics). Deng et al. (2017) examined the in vitro outcomes of *Punica* peel on Pca cells and further provided evidence for its application to inhibit the Pca growth and metastasis. The study was inspired by Venclexta, a drug used to treat chronic lymphocytic leukemia (CLL), approved by the US FDA on April 11, 2016. Venclexta is a Bcl-2 inhibitor that specifically targets the apoptosis pathway in prostate cancer cell lines, DU145, PC3, and the mouse prostate cancer cell TRAMP-C1 (Ng and Davids 2014; Deng et al. 2017). HPLC analysis showed the presence of two compounds, namely punicalagin (PG) and ellagic acid (EA), with a molecular weight of 1083.0 and 301.0, respectively, as determined by mass spectrophotometry. The viability of cells was evaluated by a routine 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) test. The morphological analysis of nuclei by Hoechst staining showed the inhibition of cell viability by the *Punica* peel extract attributed to apoptosis. The content of punicalagin (479.8 mg/g) and ellagic acid (7.5 mg/g) in *Punica* was recorded based on the regression equation and the relevant area under the curve (AUC) of each factor. The antiproliferative effect was significantly seen in TRAMP-C1, compared to DU145 and PC3 cells. The results also showed a reduced expression of anti-apoptotic Bcl-2 and amplified expression of cleaved caspase-3 and pro-apoptotic Bax posttreatment, indicating mitochondrial dysfunction causing

apoptosis. *Punica* peel treatment also showed decreased mitochondrial transmembrane potential and ROS production. The results also indicated that after treatment with peel extract, the expression levels of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) in TRAMP-C1 were significantly suppressed and tissue inhibitor of metalloproteinases-2 (TIMP2) was upregulated indicating the inhibition and invasion, the two important steps in cancer metastasis. Therefore, the study clearly demonstrates that the *Punica* peel presents a clear inhibitory effect on the growth and viability of prostate cancer cell lines.

A subcutaneous xenograft of human prostate cancer cells (PC-3) in nude mouse models was established by Ma et al. (2015) to observe the antiproliferative and apoptotic effects of pomegranate peel polyphenols. Pomegranate peel helped in shrinking tumor dimensions and mass in tumor-bearing nude mice, and significantly enhanced the rate of apoptosis. In addition, tumor necrosis factor (TNF)-α was amplified and vascular endothelial growth factor (VEGF) in serum was decreased. The study showed the antitumor activity of three polyphenols ellagic acid, gallic acid, and punicalagin found in pomegranate peels.

A plethora of literature has described the association between inflammation and prostate carcinogenesis (Kohnen and Drach 1979). The nuclear factor-κB (NF-κB) pathway is one of the well-established signaling pathways that arbitrate cancer-related inflammatory responses (Baldwin Jr 2001). Contagious NF-κB activation has been learnt in breast, cervical, liver, melanoma, and prostate cancers. Importantly, constitutive activation of NF-κB in primary prostate cancer specimens represents an independent risk factor for tumor recurrence after surgery. Rettig et al. (2008) indicated the suppression of NF-κB signaling followed by *Punica granatum* peel extract treatment in both in vitro and in vivo prostate cancer models (Rettig et al. 2008). In vitro stimulation of apoptosis by peel was demonstrated and found to be dependent on the inhibition of NF-κB activity. For in vivo studies, SCID mice implanted with LAPC4 prostate cancer peel impedimented (delayed) the emergence of LAPC4 androgen-independent xenografts in castrated mice through cell proliferation inhibition and apoptosis induction.

10.4.4 Pomegranate Peel Against Skin Cancer

Skin cancer prevalence has increased among light-skinned populations and artificial tanning devices have significantly contributed to this increase over the last three decades (http://www.who.int/bulletin/volumes/95/12/17-021217/en/. Accessed 12 Dec 2018). One in five Americans is prone to skin cancer in their life span according to the American Skin Cancer Foundation Statistics (http://www.who.int/uv/faq/skincancer/en/index1.html. Accessed 12 Dec 2018). Increasing incidence of skin cancer provide a strong basis for chemoprevention with natural remedies. Aslam et al. (2006) first reported the ability of the aqueous fraction of pomegranate peel to advance propagation and procollagen synthesis and MMP-1 inhibition in organ cultures developed from punch biopsies of sun-confined hip skin attained from adults.

10.4.5 Pomegranate Peel Against Thyroid Cancer

Thyroid cancer is a cancer of the thyroid glands and is of four different types—papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC). The thyroid cancer survival rate, especially PTC, is relatively higher than any other malignancy. Thyroid cancers are majorly treated with surgical procedures that profusely affect the patient's quality of life and it also requires patients to adhere to stern indications and contraindications. All these abovementioned conditions call for latest clinical interventions in thyroid cancer treatment. The earliest evidence for the utilization of pomegranate peel in the prevention and treatment of thyroid cancer came from studies carried out by Li et al. (2016). They evaluated the effect of pomegranate peel on thyroid cancer cells, such as BCPAP (harboring BRAF V600E mutation), TPC-1 (harboring RET-PTC rearrangement), and Nthy-ori 3–1 (human thyroid follicular epithelial cell line). The outcome of the study showed a significant decrease in the propagation of thyroid cancer cells in a time- and dose-dependent manner.

The preliminary mechanism was identified to be the induction of intrinsic apoptosis by Bcl-2 and Bax proteins and a decrease in mitochondrial membrane potential by PG and EA. Similar studies were conducted by the same group in vivo in the BCPAP tumor model in BALB/c athymic mice. *Punica* peel (dosage of 125 mg/kg/d) showed antitumor activity with 69.8% inhibition of tumor growth, improved the expression of cleaved caspase-3 (CC-3), and suppressed the expression of Ki-67 (a protein) in cancerous tissues in comparison with the untreated groups. Thyroid cancer can also metastasize to the lymph nodes and lungs. Restraining the tumor cell from migrating and invading other organs is a useful approach to inhibit metastasis, and *Punica* peel significantly downregulates the expression of MMP-9, which is one of the important proteins in the focal adhesion kinase (FAK)/MMP pathway, a vital pathway in tumor assault/invasion and metastasis.

10.4.6 Pomegranate Peel Against Osteosarcoma

Osteosarcoma is a high-grade primary skeletal sarcoma and is characterized by the deposition of immature osteoid matrix by mesenchymal spindle cells. In a study by Li et al. (2014), a homogeneous acidic polysaccharide was isolated from the pomegranate peel and its antiproliferative activity against human U-2 osteosarcoma (U-2OS) cells examined. The same study also elucidated the chemical composition of a pomegranate peel. It was shown to contain total sugar (72.4%), uronic acid (19.5%), and a negligible quantity of protein (9.7%). Further, the pomegranate peel was effective in inducing the arrest of G2/M phase, encouraged apoptosis, and hindered the growth of U-2OS cells in a dose-dependent manner. Western blotting analysis displayed that the pomegranate peel elicited the mitochondrial-mediated apoptosis, which was evident from the elevated levels of Bax/Bcl-2 ratio, release of cytochrome c, triggering of caspase-3 and caspase-9, and cleavage of poly-(ADP-ribose)-polymerase (PARP) in U-2OS cells.

10.5 Punicalagin and Ellagic Acid Isolated from Pomegranate Peel with Anticancer Potential

Punicalagin (PG) and ellagic acid (EA) are the two major constituents of pomegranate peel. Studies by Zahin et al. (2014) have clearly demonstrated in vitro antimutagenic and antiproliferative effects of these compounds in human lung cancer cells. Ellagitannins are the abundant polyphenols present in the peels of pomegranate. Punicalagin, a unique ellagitannin of pomegranate, has the capability to be hydrolyzed to ellagic acid ending in prolonged release of ellagic acid into the blood after the ingestion of pomegranate peel. It is known to be the largest polyphenol, having a molecular weight greater than 1000 g/mol. Punicalagin is most abundant in the peel/rind, compared to seeds/fruit (Lu et al. 2007). Structurally similar to gallagic acid and ellagic acid moiety, punicalagins are attached to glucose and exist in two reversible anomer types, i.e., α and β forms. Punicalagin can inhibit sulfoconjugation (Saruwatari et al. 2008) and has antioxidant (Sun et al. 2016), antiproliferative, antigenotoxic, antiviral, antiplasmodial, and immunosuppressive activity (Aqil et al. 2012; Sharma et al. 2017). Ellagitannins are also metabolized into bioactive urolithins by gastrointestinal (gut) microbiota, which conjugate in the hepatic lobes and are urinated out. These urolithins are known to reduce prostate cancer intensification (Heber 2008).

Ellagic acid (EA) is a polyphenolic molecule present in a variety of vegetables and fruits, and pomegranate peel is one among them. It is usually believed as an antioxidant. Clinical tests with EA on cultured cell lines (Human) revealed the prevention of denaturation of the p53 gene. Further, another study proposed that one of the mechanisms by which EA hinders mutagenesis and carcinogenesis is by the development of adducts with DNA, camouflaging binding sites from the mutagen or carcinogen (Sharma et al. 2017). The advent of next-generation sequencing techniques has improvised the overall understanding of biosynthesis of secondary metabolites in different plant species. The whole genome sequence and transcriptome of pomegranate peel reveal the pathway of biosynthesis of ellagitannins in pomegranate, explained by Qin et al. (2017). As reviewed all through, researchers from different regions of the world have indicated that the pomegranate peel and its chemical constituents like punicalagin and ellagic acid are effectual in hindering vital pathways at various stages of carcinogenesis, as depicted in Fig. 10.2.

10.6 Toxicity and Stability of Pomegranate Peel

Previous in vivo as well as in vitro studies prove that there is no adverse toxicity pomegranate peel on mammals, and it was also shown that in Wistar mice the intraperitoneal (i.p.) LD_{50} of aqueous extract of peel is 1321 ± 15 mg/kg (Qnais et al. 2007). The comparative study of median lethal dose (LD_{50}) for pomegranate peel extract revealed that the oral LD_{50} was more than 5 g/kg body weight (b.w.) and the i.p. LD_{50} in rodents, such as rats and mice, were 217 mg/kg b.w. and 187 mg/kg b.w., respectively. A dosage of 600 mg/kg/day of pomegranate peel extract was a NOAEL (no observed effect level) identified through a protocol of subchronic administration

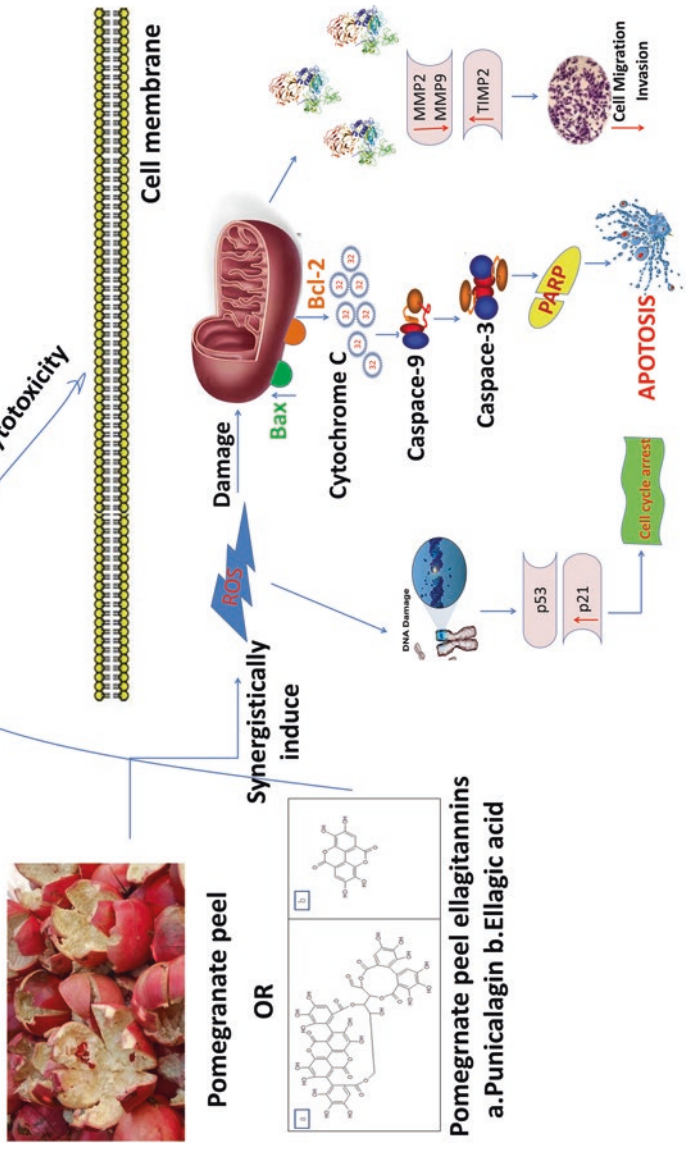

Fig. 10.2 Overall mechanisms of action of the pomegranate peel and its constituents

for a 90-day period (Patel et al. 2008; Eleonora et al. 2015). The first evidence of the possible genotoxicity of pomegranate peel used in folk medicine indicated no visible mutagenicity at the dose of 1–3 g/kg b.d. for 3 days in bone marrow cells (Sanchez-Lamar et al. 2008). The liquid extract of pomegranate peel was found to be stable at high temperatures of sterilization and at cold storage temperatures (Qu et al. 2013).

10.7 Clinical Studies

Around 13 clinical trials can be accessed from https://clinicaltrials.gov/ search page using the search term "pomegranate and cancer." One of the clinical trials was terminated for different reasons, six have been completed, three of each have been inactive, nonrecruiting, and of unknown status. Clinical trials with pomegranate peel in cancer are greatly lacking, despite the impressive amount of in vitro and preclinical studies, revealing its anticancer activity with no visible toxicity.

10.8 Conclusions

In the present scenario, employing dietary agents or functional foods for the prevention of cancer is a promising arena of oncology. The complementary and alternative medicine has drawn the attention of both clinical scientists and the general public due to dietary agents like pomegranate fruit and its waste product peel, having verified with their ability to avert or restrain cancers, their low cost, and trouble-free availability. Nevertheless, the present challenge lies in establishing the key compound or constituent of these functional foods liable for the anticancer consequences and the systems through which they stifle cancers. Scientific explorations grant ample amount of substantiations related to the bioactivities of pomegranate peel and its derivatives (products) with a focus on their anticancer features. Reports suggest promising chemopreventive/chemotherapeutic agents in pomegranate peel by exerting antioxidant, antiproliferative, anti-apoptotic, antimutagenic, and antitumorigenic effects by mitochondrial signaling pathway modulations. A significant amount of research reveals the in vitro efficiency of pomegranate peel against malignancy and promotion of cancer; however, in vivo and human trials are essential to authenticate the independent or existing therapies combined with the use of pomegranate peel against various cancers, such as breast, hepatic, prostate, skin, and thyroid cancers. It is anticipated that the chapter will provide inputs for the scientific community on the ongoing and further experimentations on pomegranate peel in cancer studies.

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