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Ancient Roots of Modern Medicines: Pomegranate

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Abstract : Research conducted in last few decades on plants mentioned in literature or used traditionally for various disease has shown in the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. The pomegranate tissues investigated in this study included history of pomegranate, pomegranate peels [PP], metabolites, uses of pomegranate in cancer disease. This review has been performed on a method of systemic narrative review on the different parts of pomegranate fruit. It also highlights the new researches on the various use and activities of pomegranate.

Index Terms -Pomegranate, primary metabolites, pomegranate peels, anthocyanin, cancer.

I. INTRODUCTION

In last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects medicinal importance of natural products those derived from plants and animals proceed human history by thousands of years. Pomegranate *[punica granatum*] is an important and interesting fruit tree that cultivated in many parts of the world. [1] ,[3] The pomegranate fruit is fleshy berry with a nearly round shape, crowned by prominent calyx. The colour of the juicy layer can vary from white to deep red various parts used as a treatments against various aliments including stomaches and bacterial infections most of the therapeutic effects of the pomegranate fruit attributed to its secondary and primary metabolites, such as polyphenols, including flavonoids, anthocynains hydrolysable tannic, fatty acids, and lipids. Pomegranate juice [PJS] are well known for their beneficial properties, they carry out antioxidant, antimicrobial, anticancer, cholesterol lowering, anti-atherosclerotic, and anti-diabetic activities as *anthocynin* – rich food, pomegranate juice have been use at various concentration to enhance the colour, taste, and aroma properties; to increase the health – benefits properties and to improve shelf lives of the fortified foods. The numerous pharmacological studies associated with the regular consumption of PJS in the fruit as a functional food. Anthocyanins, ellagic acid derivatives, and hydrolysable tannic were detect in pomegranate juice as responsible for antioxidant activity. Anthocyanins are important flower and fruit pigment; they ttrct pollinators and seed disperses and protect plant tissues from photo-inhibition and oxidation resulting from *photosynthesis.*In pomegranate fruit has been reported that the peel in particular possess relatively higher antioxidant activity than seed and pulp. Ant oxidation is one delaying the onset of major degenerative diseases. The pomegranate was mentioned at the pharaohs and used to treat intestinal worms the pomegranate flower used to treat stomach ulcers and was used to treat chronic diarrhea and treatment of cancer. Overall pomegranate has been used for thousands of years for various diseases as a medicine [2]

II. EARLY HISTORY OF NATURAL ORIGIN

The oldest medicinal manuscript, written in Mesopotamia, circa 2600 B, had documented thousands of clay tablets in *cuneiform myrrha*, and *papaver somnifera* which are still used in treatments of illness; extending from minor cough to sever inflammation and infections. The ancient *Egyptian,ebers papyru*, dated around 1500 Bc, documented thousands of complex medicinal prescription and the use of more than hundreds of natural products including aloe vera,boswellia carteri, and *ricinus communis* .[31]
over the same millennia, natural products derived medicines were already flourished in the orient. Ayurvedia- written on the holy pulp of betula utilis presumed to be the oldest written medicinal manuscript which described thousands of medicinal herb—précised in millions of poetic hymns. Simultaneously, sushruta [circa 600 BC] renowned Indian physician and surgeon of those millennia, apart from using surgical practices, also reported the medicinal importance of plants and animal species. Comparatively, these is very little known about any written earliest manuscripts of ancient Chinese herbal medicine but the most eminent encyclopedia of 'chinese material medica' listed around 6000 drugs , among them 4800 therapeutic agents are from plant origin. In Chinese medicine medicine, the species like coptidis rhizome and *evodia rutaecarp*, known as *zuo jin* wan, have long been used to treat gastric

disorders but recently it has been envisaged that these activities could because of berberine, calystigine, limonene, *rutecapine* and obacunone which are the potent inhibitors of entric microflora – helicobactor pylori. More important these plant species are still used as a frontline antibiotics and anti ulcers agents moreover, in ancient Chinese medicine, *qian ceng* ta [*huperzia serrate*] used for many centuries to treat fever and inflammation , though it has no any antipyretic or antiinflamatory properties, but a potent inhibitor of acetyl cholinesterase enzyme and hence approved to treat the *alzeheimer disease.* [30]

III. HISTORY, NAMING OF POMEGRANATE

Botanically, the pomegranate *[p. grantum*] is the subclass rosidae, order fruit such as the guva [*psidium sp*.] and feijoa [feijoa *sp*.] however, pomegranate is unusual in being one of only two species in its genus, punica which is the sole genus in the family *punicaceae*. Recent molecular studies suggest a taxonomic reconsideration might place punica within the *lythraceae* [Graham et al., 2005] . the second species in punica, p. protopunica, is found only on the island of Socotra ,of the Arabian peninsula, and is considered an ancestral species or an independent evolutionary path. The name *punica* is the feminized roman name for cartages, the ancient city in northern Tunisia from which the best pomegranate came to Italy.[4]

The pomegranate is one of the 'seven kinds' mentioned in the bible, the *Koran*, and in *Buddhist and Chinese* arts. It is estimated that pomegranate might have been introduced into culture about 5000 years ago. In different regions of the natural habitat of wild pomegranate, the period time between the first appearance of the modern type of human and the transition of their different populations to agricultural activities is anywhere between 2000 and 6000 Bp. [6]

According to the available records, seafaring in the ancient Mediterranean began more than 10,000 years ago and evidence of the depends on ship to transport merchandise is reflected in texts dating from the end of the 4th millennium B.P. a ship carrying the finest luxury goods of the late bronze age sank off the coast of ulu burum, *turkey*, in the late 1400 B.P. its discovery yielded great insight into cultural life during *egypt's* 18th dynasty and the LH IIB period in *Greece*. The ship contained ceramic containers in which more than 1000 archaeo botanical evidence from military sites shows that it was brought to central Europe by roman solders during their occupation of this areas and thus, it remained an important luxury item. In addition to the symbolic nature of pomegranate, its chemical properties made it useful for a no. of widely disparate purposes, ranging from perfume ingredients from pliny's natural history included pomegranate rind, while its juice was used as an astringent to prepare oil to get a scent. It was highly valued fruit during the late bronze age Ironically however, pomegranate peels rinds were included in recipes for different medicinal purposes during classical and medieval times. Use of pomegranate as a medicine is mentioned in ancient Greek medical papyrus by Rbers, which represents a complied reference book of the 16th century Bc. Even plinii emphasized that it had been considered a universal therapeutic agent and used by the prominent medical healers of the ancient world and middle ages viz. hypocrite, galen, oribasii, paul eginski, joven damaskin, er-razi,joven-iben-mausa IBN sinn. In folk medicines of the orient, Mediterranean and Africa, it is included in 32 out of 56 groups of pharmacological and therapeutic treatments, 14 out of 17 pharmaco therapeutic groups of plants, used to treat diseases related to 15 out of 16 classes diseases according to the international. Classification.[5], [7],[8]

IV. MATERIAL AND METHODS

Pomegranate fruits of *Kurdistan* cultivates were selected from halabja garden. Sweet pomegranate [punica grantum cv assaria] were harvested in a commercial orchard in eastern algrave fruits were transported on the same day to the laboratory at the university of algrave. The selected plant material were harvested during nov.2018 at the field located in noto.

The harvest was performed according the ripping stage, about 180 days after full bloom samples were taken from 12:00h to 14:30h after picking fruits were immediately transported to the laboratory. Each fruit was carefully cut at the equatorial zone with a sharpened knife, and then intact arils were manually obtained from whole fruits and the juices (1mg accuracy on balance), weight of the arils per fruit, juice yield (%) and the colour of juices by colorimeter Minolta CR 400 (Konica Minolta, Milan, Italy) were determined .

3.1 standard reagents and chemicals

Various chemicals present in different parts of pomegranate plant like peel, root, bark, flower, leaves and so fourth exhibit different phytochemicals are as follows:

A) Pomegranate peels

1) Gallic acid
2) Ellagic acid
3) Punicalin
4) Punicalagin
5) Caffeic acid
6) Ellagitannis
7) Pelletierine alkaloids
8) Luteolin
9) Kaempferol
10) Quercetin

B) Pomegranate juice
1) Simple sugars
2) Aliphatic organic acid
3) Gallic acid
4) Quinic acid
5) Flavonls
6) Amino acid
7) Minerals
8) EGCG
9) Ascorbic acid

C) Pomegranate root and bark
1) ellagitannis
2) piperdine alkaloids
3) pyrrolidine alkaloids
4) pelletierine alkaloids

D) Pomegranate flower
1) Gallic acid
2) Ursolic acids
3) Triterpenoids
4) Fatty acids

E) Pomegranate leaves
1) Carbohydrate
2) Reducing sugars
3) Sterols
4) Saponins
5) Flavonois
6) Tannis
7) Piperidine alkaloids
8) Flavones
9) Glycosides
10) Ellagitannis

F) Pomegranate seeds
1) 3,3' di-o methylellagic acid
2) 3'3',4'- tri-o methyallagic acids
3) Punicic acids
4) Oleic acids
5) Palmitic acids
6) Steric acids
7) Linolic acids
8) Sterols
9) Tocopherols
10) Sex steroids

Reagents like- delphidinnidin 3,5 diglucosides, delphinidine 3- glucosides, cyaniding 3,5 diglucose, cynidine 3- glucoside, palargonidin 3,5- diglucoside standards were purchased from apin chemicals ltd,uk. Methanol was purchased from sigma-aldrich quimica, SA (spain). Formic, oxalic, tartaric, pyruvic, malic, ascorbic, maleic citric, fumeric and sulphuric acids glucose and fructose were purchased from *riedel-de-haen* (germany). The ultrapure water was purified with the millq system.

3.2 Primary metabolites and anthocynnis

In pomegranate contains primary and secondary metabolites such as polyphenols, including flavooids, anthocynains and hydrolizable tannis, fatty acids, and lipid.

Sugars

The pomegranate fruit is a rich source of sugars the level of the sugars in pomegranate juice is highly correlated with the level in the juice ranges from 4.2 to 8.5 g/100g depending on cultivars, climatic conditions, and cultural techniques. Pomegranate juice contains, a high amount of polyphenols such as flavonoids , ellgitannis, and the colour molecules anthocyanins sugars found in the fruit peel were in some controversy among studies from different countries. It should be noted that those studies were done for different purpose and therefore followed different procedure of extraction and detection

Organic acids

Analyses of the organic acids of pomegranate aril juice have shown that citric acid is generally the predominant organic acid and its content can reach up to 3.76 g/100g in the juice in addition, it contains significantly lower levels of malic, oxalic, succinic, and tartaric acid ascorbic acids in the fruit peel, citric acid is the predominant organic acid and its content can reach up to 1.68/100g smaller amounts of mallic, succinic, and oxalic acid were detected in peels.[27]

Amino acids

Amino acids have an important role in protein biosynthesis and secondary metabolites syntheses addition to their role as building blocks of protein, amino acids functions as precursors or intermediates in biosynthetic pathways such as production of colour molecules and volatiles in fruits, energy release through degradation, signaling and plant stress response there are very limited data and only a handful of research publication concerning amino acids in the pomegranate fruit.[22],[23]

Proteins

The data on proteins in pomegranate fruits are limited and mainly concern total protein content in various tissues most of the studies do not report specific protein functions with the exception of storage proteins in the seeds and lipids transfer protein in the arils in general, the percent of total proteins in pomegranate juice is usually low, from < 1.0 to 1,1, which is quite a narrow range diversely, percent of total proteins in pomegranate seeds varies from 4.1 to 16.9% which is quite a wide range.[24]

Lipids

The lipids are a group of small hydrophobic molecules that include fatty acids, waxes, sterols, fat soluble vitamins, phospholipids, mono-di and triglycerides primary and secondary lipids have diverse functions in living organisms, including energy storage , cell signaling, nutrition, hormones, transport and structural components of cell membranes. the most lipid rich fraction in pomegranate is the seed, which contribute 10% to fruit weight generally, seed oil constituents 6-20% of seed weight and contains a large quantity of lipid.[17]

The chain length of the lipids is divided to three classes; medium- (C6-C12), long – (C14-C20), and very long (C22 and C24). The total lipid (the term refers to primary and secondary lipids) percentage in seeds varies from 4.4 to 27.2% [9],[13],[10],[25]

3.3 Anthocynnis

Anthocyanins is a secondary metabolites in pomegranate juice anthocyanins (ACNS) are the largest and most important groups of flavonoids present in pomegranate juice and together with hydrolysable tannis (HTS) they constitute the most valuable bioactive compounds chemically, ACNS are glycosides of polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium or flavyium salts. It is the key colour molecules of pomegranate present in various parts of the pomegranate trees, including leaves, flowers, and fruits. The pomegranate fruit is a rich source of anthocyanins and produces several derivatives of anthocyanins these secondary metabolites accumulate in all fruits tissues and mainly in the edible part of the fruit, the arils and in the fruit peel all six anthocyanin pigments were detected in pomegranate cultivates from different geographical regions, which include israleli, turkesh, Spanish, Californian, tunsian, Italian and Chinese pomegranate.[26]

The function of anthocyanin in the biology of the pomegranate tree is not yet fully understood the tree of the 'white' phenotype pomegranate varities, which do not produce any anthocyanin, in vigorous and fertile. It seems, however, that the white flowers antocyanins less fruits are more susceptible to browning and radiation damages. [19]

Composition of anthocynnis in peels

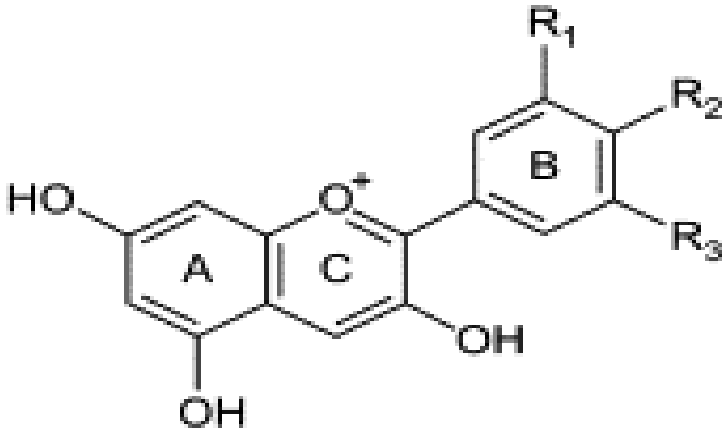
It an attempt to determine the colour variability among pomegranate varities, 29varities that represent most of the phenotypic variability in the Israeli pomegranate collection were assays. Total anhocyanin levels were measured for both peel and aril extract. the content of total anthocyanins in the peel varied between 0.2 and 8.0x 10mg/l, while the anthocynin content in the aril juice varied between 0.2 and 3.5x10 mg/l. [15], [16].

Composition of anthocynnis in juice

While most Israeli and Mediterranean cultivars displayed negligible levels of delphinidines , and cyanidins were the major anthocyanins in their aril juice inIsraeli cultivars delphinidine derivatives content of the aril and cyanidines could reach about 60% of the total anthocyanins in the aril juice . juice from fruit of 30 varieties grown in Tunisia were studied for their anthocyanin content. The total anthocyanin content was diffffferent among varities and ranged from 9 to 15 mg/l juice. [20]

From these studies of different varieties originating from several regions in the world and from many others not reported here; it is evident that there are significant quantitative and qualitative in the anthocyanins content of peel and juice between pomegranate varieties.

Anthocyanins act as free radical scavengers, tanks to the o-diphenol substitution in ring B of anthocyanins and the conjugated double bond system, stabilizing radicals due to hydrogen donation metal chelation or DNA protein bonding are important in biological systems. Deliphinidin, cyaniding and pelargonidin glycoside are the most representative anthocyanins in PJS with strong antioxidant activities [21]



Basic chemical structure of anthocyanins

I. Use of peels

Pomegranate peel are useful for various disease. Pomegranate peels are typically discarded and thought of as inedible, but they're used regularly for various health and beauty benefits in ayurvedic medicines an alternative practice with roots in Indian culture pomegranate peels are high in antioxidant and polyphenols and they have been shown to treat hyperpigmentation, a condition characterized by dark patches of skin.[11]
Pomegranate peels may protect may against UVB rays and improve hyperpigmentation, acne, signs of aging and wound healing. Pomegranate peels contains high amounts of punicalagin a polyphenol that has been shown to have anti-cancer properties in some test-tube studies. In one such study, pomegranate peel extract was found to be a promising treatment for prostate cancer because of its ability to induce the death of cancer cells. [12],[14]

Background – The health promoting activities are attributed to the high concentration of polyphones found mainly in the fruits peels, which posses about 300-fold more polyphenols and 40- fold higher antioxidant activities than arils, the edible section these polyphenols act as scavengers of reactive oxygen species (ROS), and are associated with a reduction in stress related chronic diseases and age realated disorders.previous studies showed that hydrolysable tannis (HTS) and anthocyanins (ATS) are predominatpolyphenols present in outer fruits peels. These compounds are also produced in vegetative tissues such as osmotic stress, drought UV irradiation and low temperature. The biosynthesis of both ATS and HTS is related to the shikimate pathway ATS were formed from the phenylpropanoid pathway that begins with phenylalkaline, an aromatic amino acid produced from the shikimate pathway which is suggested to be produced from an enzyme in the shikimate pathway. HTS biosynthesis starts from gallic acid (GA) which is suggested to be produced from an enzyme in the shikimate pathway, shikimate dehydrogenase (SDH) reaction in the shikimate pathway. A previous study showed that '*vitis vinifera'* has four isoenzymes for DQD /SDH which have different affinity to the cofactors NADPH+. Moreever, analyses of enzyme activities suggest that VvSDH4 can produce GA

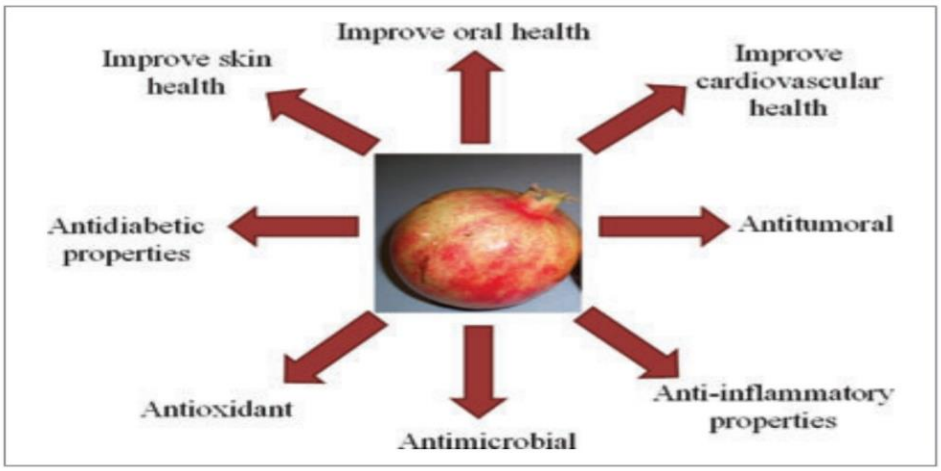


Figure 4–Principal functional and medicinal effects of pomegranate.

Oxidation / reduction mechanism of antioxidants

Antioxidation is one of the most important mechanisms for preventing or delying the onset of major degenrative diseases. Active oxygen (hydroxyle,peroxy radicals, and singles oxygen) is highly toxic and one of the strongest causative agents of many diseases, including cancer, heart diseases; contracts and cognitive disorder. Antioxidants block the oxidation processes that contribute towards these chronic diseases and delay the onset of degenerative diseases of aging.[11]

Oxidation /reduction mechanism

1) Oxidative stress } endogenous source of ROS/RNA mitochondria poroxisomes
exogenous source of ROS/RNA radiation ozone

2) defense system - enzyamatic superoxide dismutase catalase
nohon enzymatic vit.E, vit.C

3.2 Mechanisms of action of antioxidants

two principle mechanisms of action have been proposed for antioxidants. First chain breaking mechanisms by which the primary antioxidant donates an electron to the free radical present in system (lipid radicals) .the second mechanism involve s removal of ROS, RNA initiating catalysts. Polyphenol compounds has ability to donate hydrogen atom and thus to act as chain breaking antioxidants, it can also chelate transition metal ions and hence inhibit free radical formation.[34].

3.4 pomegranate peel extract as an inhibitors of SARS-COV-2 (COVID -19)

The active compounds within plants extract are mainly secondary metabolite that can be classified into four main categories according to their different chemical properties and structures terpenoids, polyphenols, nitrogen and sulfur containing compounds. [32].

Polyphenols are the largest and the most widely distributed group of bioactive compounds in the plant kingdom they have a distinctive structural skeleton consisting of one or more aromatic phenyl rings connected to hydroxyl groups and exhibiting a wide spectrum of health related inflammatory, anti-allergic, anti- antherogenic, and anti cancer. Moreover, several studied demonstrated the antiviral potential of some classes of polyphenols against eptein barr virus, enterovirus, herpes simple virus (HSV), influenza virus and other viruses causing respiratory tract-related infections. The mechanisms underpinning the antiviral activity of polyphenols are varied and include the inhibition of the virus entry because of their permanent attachement on the virion envelope or the inhibition on of thr enzyme responsible for the virus replication. The severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) is a zoonotic pathogenic virus identified for the first time in December 2019, responsible for one of the most serious pandemics in human history, the coronavirus disease 2019 (covid-19) so far, the number of covid-19 cases have amounted to over 60 million people with more than 1.4 million deaths from all over the world. SARS – CoV-2, like other coronaviruses, is an enveloped positive – sense single standard RNA virus exposing a highly glycosylated spike (s) protein on its surface, which facilates the viral entry into host cells. Entry depends on the binding of the surface unit S1 (a portion of the s protein) to a cellular receptor, facilating viral attachment to the surface of target cells. [33]

3.4. Cancer

Cancer is the second leading cause of death in the united states, and those who survive cancer may experience lasting difficulties, including treatment side effects, as well as physical, cognitive and pshychosocial struggles.

The pomegranate constituents are shown to modulate transcription factors, pro-apoptotic proteins, anti- apoptoic proteins, cell cycle regulator molecules, protein kinase, cell adhesion molecule, pro-inflammatory mediators, and growth factors in various cancers.Pomegranate has also been shown in preclinical studies, to boost the effectiveness of certain chemotherapy drugs the while protecting against their harmful side effects. [18]

How pomegranate fights cancers in addition to preventing cancer from developing , in preclinical studies, pomegranate has shown multiple effects that help block the growth of existing cancer cells and prevent them from spreading these effects include 4,5 blocking the cells cycle. Pomegranate can shut off a cancer cells ability to divide, limiting its growth by affecting multiple genes related to the cell cycle however, it does not block healthy cells from dividing normally inducing cell death compound in pomegranate directly cause cancer cell to die by including apoptosis. Cancer cells require new blood vessels in order to support their growth with an ample blood supply pomegranate blocks growth factors related to angiogenesis, which limits the formation of new blood vessels in tumors. Cancer cells are often able to separated from cells and migrate through tissues, eventually spreading to distant organs in the body pomegranate limits cancers cells ability to spread by affecting gene expression related to invasion, migration and met astasis. Pomegranate is also being exported as an adjuvant to conventional cancer treatment like chemotherapy it has been shown to bolster the effect of such treatments , white also deleterious side effect.[28]

3.5 Pomegranate and breast cancer

Breast cancer is the second leading cause of cancer related deaths in women in 2016, an estimated 246,660 new cases of invasive breast cancer are expected to be diagnosed in women in the united states, along with 61,000 new cases of non-invasive breast cancer it regards as one of the important type of cancer, which is common in female especially in the united states. Breast cancer is type of tissues cancer that mainly include an inner layer of milk glands or lobules and ducts. [35].
Breast cancer starts in the cells of the breast a cancerous tumor is a group of cancer cells that can grow into and destroy nearby tissues. It can also spread to other parts of the body cells in breast sometimes changes and no longer grow or behave normally these changes may lead to non-cancerous (begin) breast condition such as atypical hyperplasma and cysts. They can also lead to non-cancerous tumors such as intraductal papilloma's however, some cases changes to breast cells can cause breast cancer. Most often, breast cancer starts in cells that line the ducts which are the tubes that carry milk from the glands to the nipple. This types of cancer is called lobular carcinoma both ductal carcinoma and lobular can be in situ, which means that the cancer is still where is started and has not grown in surrounding tissues. They can also be invasive, which means that they have grown into surrounding tissues. Less common types of breast cancer can also develop these include inflammatory breast cancer, paget disease of the breast and triple negative breast cancer.[36],[37].

3.6 conclusion

In this review we observed the various useful parts of pomegranate and also the pomegranate used in different diseases like diabetes, heart disease, rheumatoid arthritis, it is antioxidant, antimicrobial, anticancer various parts of pomegranate like peels, leaves, juice are used. Pomegarante used from ancient days that's why it is called ayurvedic fruit and it contains high metabolites.The primary metabolites and secondary metabolites are helpful to our body like sugar, amino acids, lipids, proteins, organic acids, anthocyanins. Pomegranate is also very useful against cancer most of the breast cancer cells it shows multiple effects against cancer cells and prevent from spreading in present study, we found that the polyphenols contains in an ethanoic extract derived from pomegranate peels inhibited the interaction between spike and ACE2, and reduced the activity of the viral 3cl protease in vitro, potentially suggesting the use of the extract as an adjuvant in the treatment against SARS-COV-2 (covid-19) infections the study here presented paves the way for longer and in depth investigation on the activity of pomegranate SARS-COV2 infections in vivo and it may also promote new ideas on how to reuse an agroindustry byproduct for valuable and healthy application.

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