MEDICINAL IMPORTANCE OF CITRUS PRODUCTS AND BY-PRODUCTS - A REVIEW

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ABSTRACT

For over 50 years of citrus research undoubtedly directed the healthful properties of citrus fruit juice and by products, an out come of waste in the form of peel and rag generated during the processing of citrus juice industry. In addition to nutritional properties, citrus fruits has numerous medicinal importance. The major thrust in addition to vitamin C has been the water soluble B - complex vitamin especially folic acid and thiamin (Vitamin B) vitamins. The citrus juice folate was reported to reduce neural tube birth defects and the risk of heart disease by lowering blood serum homocystine level. Therapeutical value of carotenoids that could be the important first line of defence against ROS and also took part in catalytic activity. It helps in the deactivation of carcinogens. Anthocyanin is a pigment having the therapeutical properties, largely employed in the pharmaceutical industry and had ability to modulate capillary permeability and resistance. Pectin is a dietary fiber reported to reduced the serum cholesterol, hypercholesterolemia and promote the excretion of fats, bile acid, cholesterol and posses growth suppression of prostate cancer cell. Limonene is a terpenoid which is the major component of citrus volatiles, produced by distillation during citrus juice processing. It has properties to block and suppress the carcinogenic events. However, another foremost thrust of citrus research programme has been the investigation of the therapeutical value of principle citrus flavonoids. Which occurs in fruits and their medicinal properties had been found to induced ability to prevent red blood cell clumping, affect the bleeding and capillary fragility, anti-inflammatory activity against allergic reactions and antiviral activity. Besides, certain citrus beverage influenced the metabolism of some pharmacological agents indicating that in recent past during the few years, a considerable amount of commercial interest has been developed on the health promoting properties of citrus fruit juice and by products.

The genus Citrus belongs to the Rutaceae and the subfamily Aurantioideae and is characterized by fruit with a juicy vesicles within segments. Major commercial citrus species include orange (C. sinensis), grapefruit (C. paradisi), lemon (C. limon), lime (C. aurantifolia), and mandarin (C. reticulata). Citrus is made up of an outer peel, which includes epidermis, flavedo, albedo, and endocarp. The flavedo in the subepidermal region contains chromoplasts (which give the fruit its green, yellow, or orange coloring) and numerous oil glands filled with aromatic essential oils. The albedo (mesocarp) is rich in pectin, cellulose, and hemicellulose. The endocarp (inner flesh) consists of segments (carna) that are filled with closely compacted juice vesicles and contain pigments, sugars, and organic acids; and are the primary source of citrus juice. Seeds may be found within the segments adjacent to the core, at the center of the fruit (Girard and Mazza, 1998). Annual global production of citrus fruits has exceeded 100 million tonnes, of which more than one third has been processed (FAO, 2000) in some of developing and even up to the 70 percent in the developed world into either juice or concentrate.

Smaller percentage of the grapefruit and lemon crops are used for juices, while tangerines and other minor citrus crops are primarily consumed fresh. The processing of citrus fruit into juice gives rise to a large volume of by-products that contain rind and pulp (Girard and Mazza, 1998).

Major effort on citrus research was undertaken worldwide in the past, during the
development of the citrus juice industry in the 1950s, to develop ways to use the huge volumes of citrus rinds generated by the juice industry. It is well known that citrus fruits and juices are healthful foods. However, the sources of citrus benefits are not well understood, and for over many years, the Citrus research directed to documenting new health benefits of citrus fruit and juices. This included an investigation of health properties of citrus products; various citrus components are currently being studied with respect to health, including phenolics, carotenoids, limonoids, and of course, vitamin C, water soluble B-complex vitamins, specifically folic acid and thiamine (vitamin B), citrus pectins as a dietary fiber, therapeutic value of the citrus flavonoids etc.

**Phenolics**

Health research on citrus phenolics has focused almost exclusively on their flavonoid components, although hydroxycinnamates do occur in these fruits. The composition and localization of these compounds are highlighted as under:

**Composition and Localization**

There are four classes of flavonoids in citrus: flavanones, flavones, flavonols, and anthocyanins (blood oranges only). The predominance of flavones and flavanones is a distinctive characteristic of citrus, while flavonols and anthocyanins are widely distributed among other fruit species (Macheix et al., 1990). More than 60 different flavonoids have been identified in citrus species (Benavente-Garcia et al., 1997). During fruit maturation, flavonoid levels have been reported to increase, decrease, and fluctuate (Baldwin 1993; Lallan Ram and Godara, 2002). Peel flavonoids form part of the resistance mechanisms of citrus, possessing antimicrobial and antiviral activity, and protecting peel by absorbing UV radiation. The flavonanes (including flavanone glycosides) are the most abundant flavonoid group in citrus, while their occurrence in other fruits is rare (Macheix et al., 1990). The flavanone profiles of citrus species are unique, and are therefore useful in taxonomic classification. Hesperidin (hespertin rutinoside) is a major flavanone component in orange, where it is localized mostly in the flavedo and albedo (i.e. peel). Naringin is the predominant flavanone in grapefruit (Ameer et al., 1996). It is found not only in the flavedo and the albedo of the fruit, but also in the core and segment membranes (Macheix et al., 1990; Girard and Mazza, 1998). Although hesperidin is predominant in orange, it is only a minor flavanone component in grapefruit. Lemon peel contains both the-hesperitin and eriocitrin (eriodictyol 7-rutinoside) flavanones (Macheix et al., 1990).

Flavonane content and profile of citrus products is of interest to food manufactures because flavanones affect taste and bitterness. The principal compound responsible for the immediate bitterness of citrus is naringin, although neohesperidin and poncinin also contribute. The limonoids have bitterness (Goodwin and Goad, 1970). Hesperidin is not soluble and thus contributes to be haze in orange and lemon juice. Although flavanones are the predominant class of flavonoids in citrus, they are probably not as important as other flavonoid classes in terms of human health (Benavente-Garcia et al., 1997). Flavones (and their glycosides) are found in lower concentration in citrus than flavanones. Flavones are localized in the essential oil of the flavedo. Examples of citrus flavones include luteolin, diosmin, and apigenin. The polymethoxylated flavonones, such as nobilixin (hexamethoxyflavone), sinenstin, and tangeretin (pentamethoxyflavones) are of particular interest since polymethoxylation is associated with more potent biological activity (Macheix et al., 1990; Benavente-Garcia et al., 1997).

The third major group of citrus
flavonoids are the flavonols (and their glycosides), which include: quercetin, kaempferol, rutin, limocitrol, limocitrin, and isolimocitrol (Macheix et al., 1990). The first three of these flavonols are widely distributed among many fruit species. The last three are found in lemon, and contain three, two, and three methoxy groups, respectively. Citrus flavonoids extracts have been manufactured by citrus processors and utilized as food supplements for human and animals health use for several decades (Girard and Mazza, 1998). The citrus-flavonoids, which are extracted from the peel, contain all three major classes of the citrus flavonoids. “Hesperidin complex,” taken from de-oiled orange peel extract, contain several flavonoids, including flavonols, flavones, and flavonones (Macheix et al., 1990).

**Water soluble B-complex vitamins**

Prior to work of Streiff (1971), citrus was not considered significant source of folic acid. However, the development of new microbiological methods of analysis allowed a more accurate determination of folic acid content, and it was discovered that not only was orange juice a good source of folate, the presence of ascorbic acid in the juice protected the folate from being destroyed by processing. The folic acid in orange juice generally ranges from 30-90 micrograms per 177.4 ml serving, which is from 7.5 to 22% of the U.S. Recommended Daily Allowance (U.S. RDA) of 400 micrograms. However, caution should be exercised in making nutritional claims due to the wide natural variation between samples. Attaway and Moore (1992) stated that for over 30 years, the Florida Department of Citrus has supported research into the health benefits of citrus juices other than vitamin C. As a result, it is now known that citrus is significant source of folate and thiamine, that citrus flavonoids have therapeutic value against allergy and other inflammatory diseases, have anti-cancer activity and beneficial effects on capillary fragility and atherosclerosis and have significant anti-viral activity.

Citrus fruit are relatively good sources of folic acid and contributed substantial amounts of folate to the diet, by virtue of the large volume of citrus products consumed. Folic acid acts as a coenzyme in numerous biological reactions, and is used to transport single carbon fragments during amino and nucleic acid synthesis. Decreased folic acid intake is linked to pathological disorders such as CVD and cancers. Severe deficiencies during pregnancy may lead to neural tube defects in offspring. Both the animals and humans in vivo studies have shown that folic acid deficiency can cause chromosomal damage that precedes cancer development (Rouseff and Nagy, 1994). Wilbur et al. (2000) reported the importance of folate to human health where it was shown to reduce neural tube birth defects by up to 75% when taken by women prior to conception and during pregnancy. Folate has also been associated with a reduced risk of heart disease by lowering blood serum homocystine levels. An 8 ounce glass of orange juice contains 10% to 25% of the 400 microorganisms recommended for daily intake in the United States, making it a good to excellent source of natural dietary folate. While folate is important to all individuals, women of child-bearing age and those at greatest risk for coronary heart disease need to be most concerned with getting enough folate in their diet.

Thiamine has also been found in noteworthy amounts in citrus juices. According to Rollers et al. (1990), the thiamine content of frozen concentrated orange juice varies from 90 to as high as 280 micrograms per 177.4 ml serving which is 6 to 18% of the presently accepted U.S. RDA of 1500 micrograms.

**Vitamins C (Ascorbic acid)**

Vitamin C is essential nutrient (i.e., a dietary component required to prevent specific deficiency-related diseases). Although the much
focus is given primarily on non-essential fruit phytonutrients, vitamin C is growth mentioning since, like phenolic and carotenoids, it functions as an antioxidant. Vitamins C is present in a high concentration in citrus fruits. Even though, only about one quarter of the vitamin C content of the whole fruit remains in the juice, a 227 ml (8-oz) serving of either grapefruit or orange juice will provide 100% of RDA intake for vitamin C (Rouseff and Nagy, 1994). After processing, vitamin C remains in the peel and pulp and especially in foods, and various processing factors have been shown to reduce its content. Neutral pH, high temperature, extended heating, and the presence of metal ions can all reduce the vitamin C content of foods, Vitamin C from citrus products is relatively stable because of low pH of citrus products, and the high content of vitamin C in these fruit in general. Vitamin C is retained better in foods that are normally high in this antioxidant nutrient (Klein and Kurilich, 2000).

As an antioxidant, vitamin C is considered to be an important first line of defense against ROS and works with other antioxidant compounds and antioxidant enzymes, such as GSH reductase and ascorbate peroxidase. Vitamin C also helps to maintain enzymes-bound metal ions in correct reduction states for catalytic activity. It is implicated in the deactivation of carcinogens (i.e., anti-initiation activity) and may impede the reaction of nitrates with amines and amides, which can form potent carcinogenic nitrosamines within the digestive tract (anti-initiation activity) (Mirvish et al., 1975). For some time, there has been considerable evidence concerning the therapeutic properties of anthocyanins present also in Vaccinium myrtillus (Bay et al., 1983), largely employed in the pharmaceutical industry, especially their ability to modulate capillary permeability and resistance (Beretz and Cazenave, 1988). On the other hand, the capacity of flavonoids to interface with the immune system has been known for a long time (Berg and Daniel, 1988). Unfortunately, these interactions are complex and still not well understood. However, today, it is clear that many flavonoids can suppress non-specific immune responses (such as macrophage, oxidant release from neutrophils, mast-cell activation). Beside, flavonoids seem to induce a stimulation, at low doses, and an inhibition, at high doses, of lymphocyte proliferation; the immunostimulatory effect is more evident in immunodeficient subjects. This kind of interaction with the specific immune system has

Anthocyanin

The red color of the orange juice from pigmented varieties of Citrus sinensis is due to the presence of water-soluble pigments which were shown to the anthocyanins in nature (Maccarone et al., 1983). Cyanidin-3-glucoside is the main components of pigments from ‘Moro’ orange juice (Maccarone et al., 1985), together with minor quantities of various common anthocyanins; besides, ‘Moro’ orange contain a large amount of these pigments than other varieties (‘Tarocco’ and ‘Sanfuinello,’ particularly), more widespread and appreciated on the market (Maccarone et al., 1985).

Carotenoids

Carotenoids are the pigments responsible for the color of citrus peel, fruit, and juice, and therefore important to the visual quality of this fruit. Lycopene is the primary pigment that color red and pink grapefruit. While α-carotene is not generally abundant in Citrus, some varieties of red grapefruit are a particularly good source. Carotenoids that can be converted to vitamin A are desirable because of its metabolic role. Sixteen carotenoids with provitamin A activity have been identified in citrus, the major ones being α-carotene, β-carotene, and β-cryptoxanthin (Roussel and Nagy, 1994).
been well demonstrated especially for cyanidol, the proanthocyanin precursor of cyanidin (Berg and Daniel, 1988). Cyanidin -3 - glucoside is the main components of pigments from 'Moro' orange juice, together with minor quantities of various common anthocyanins. On the other hand, the capacity of flavonoids to modulate capillary permeability and resistance and to interface with the immune system has been known for a long time. The recent study demonstrated that the inclusion of the 'Moro' orange juice in the rat diet can induce a protective effect on the blood vessel wall and gastric mucosa; in addition, it seems to elicit an immunostimulatory effect, (Saija et al., 1992).

Pectin

Citrus fruits contain pectin, cellulose, and hemicellulose. All of these compounds are resistant to breakdown by digestive enzymes, and therefore are sources of dietary fiber. Pectin is the fiber source in greatest abundance in citrus, and is present in both the edible and inedible portion of the fruits. Greater amounts of pectin occur in the fruit solids, such as the albedo (peel), juice sacs, and membranes, as compared with the juice, but the bitterness and astringency of these high pectin components limits their use in citrus products. Pectin is beneficial to human health by regulating blood sugar levels and reducing serum cholesterol. It regulated blood sugar by both delaying gastric emptying and increasing the intestinal mucosa. This slows the uptake of glucose into the serum and the concomitant rise in insulin. Pectin may also be useful as a dietary aid in managing non-insulin dependent diabetes.

The benefits of grapefruit pectin, as a dietary fiber have been investigated for over 12 years by a medical team at Funda and found that citrus pectin has very beneficial effects with regard to serum or liver cholesterol levels and may even prevent or postpone the onset of atherosclerosis. Similarly, using microswine, Baekey et al. (1988) reported that grapefruit pectin significantly lowered plasma cholestrol, nearly 30% and improved the ratio of low density lipoprotein to high density lipoprotein LDL/HDL ratio by 31% compared to the non-pectin high cholestrol fed pigs. In other study diet supplemented with grapefruit pectin showed 85% decrease in plaque formation on the surface area of the aortas and an 88% decrease was observed in the narrowing of the coronary arteries. This study concluded that not only does grapefruit pectin lower plasma cholestrol, but it also reduces the formation of plaque in the major arteries which causes atherosclerosis.

Cerda et al. (1988) studied the possible effect of pectin on human cholesterol using a group of patients, unwilling or unable to alter their lifestyle. Using a 16-week, double-blind crossover study with 32 volunteers screened for high cholesterol levels, they demonstrated a 7.65% decrease in plasma cholesterol, a 10.8% decrease in low density lipoprotein, which is the most abundant cholesterol-carrying lipoprotein in human plasma, and a 9.8% decrease in the ratio of low density lipoprotein to high density lipoprotein in the pectin supplement compared to that of the placebo. Since previous clinical trials have indicated that each 1% reduction in blood cholesterol level yields approximately a 2% reduction in risk for coronary heart disease. Further study showed that grapefruit pectin, without change in current lifestyle and/or diet, can significantly lower plasma cholesterol levels and produce a significant improvement in LDL/HDL ratio in human patients (Cerda et al., 1988). It was addition of 3% grapefruit pectin to an atherogenic diet significantly lowers cholesterol in microswine with established high cholesterol levels (Cerda, 1991) and also showed a significant difference in the amount of coronary artery narrowing, favouring the grapefruit pectin atherogenic diet in all
instances. Other study revealed that grapefruit pectin retards the development of atherosclerosis, even in animals with established high cholesterol levels. This research is most significant as it demonstrates a definite effect of citrus pectin on the disease of atherosclerosis, and not just a symptom such as blood cholesterol. These findings are important for people with established atherosclerosis, who at present can only look forward to coronary bypass surgery for their treatment. If pectin can regress atherosclerosis, there could be considerable demand for its use in both pre and post heart bypass patients in order to prevent and reduce atherosclerotic plagues through this relatively simple substance. Grapefruit pectin has been shown to lower serum cholesterol levels in human subjects and to reverse atherosclerosis in animals.

Pectin supplementation protects against CVD by reducing serum cholesterol. In both diet-induced (in rats) (Vorster, 1984) and genetically predisposed (in minipigs) (Ahrens et al., 1986) hypercholesterolemia, symptoms were reduced with pectin supplementation. Pectin may also promote the excretion of fats, bile acids, and cholesterol (Baker, 1994). Modified citrus pectin was reported to have beneficial effects in specific in vitro assays used to detect growth suppression of rat prostate cancer cells (Hasieh and Wu, 1995).

Limonene

Limonene, a terpenoid, is the major component of the Citrus volatiles, which are made up almost entirely of terpene hydrocarbons. Limonene, which is obtained by distillation during citrus juice processing, has been shown to block and suppress carcinogenic events. The addition of limonene or limonene-rich citrus oils (orange, lemon, grapefruit, or tangerine) to a semi-purified diet induced GST S-transferase activity in the liver and small bowel mucosa. Feeding resulted in inhibition of forestomach, lung, and mammary tumors (Hocman, 1989; Wattenberg et al., 1986). Limonene has also been shown to inhibit the conversion of proto-oncogenes to their activated farnesylated forms, in both in vitro cell cultures and in vivo mammalian systems (Crowell et al., 1991; Wattenberg 1983; Maltzman et al., 1989).

Flavonoids

Another thrust of Citrus research programme has been the investigation of the therapeutic value of the principal flavonoids of citrus. Flavonoids occur in all fruits and vegetables and their medicinal properties have been found to induce ability to prevent blood cell clumping, to affect capillary fragility, antiviral activity. During the few years, a considerable amount of commercial interest has developed on the health promoting properties of citrus flavonoids which are given as under:

a. Anti-inflammatory and anti-allergic activity

Those who suffer from hay fever and other allergic reactions, know that the release of histamine is a feature of these disorders, and that compound known as antihistamines have been used in their treatment for over 40 years. Middleton and Drzewiecki (1982) studied the effects of naturally occurring flavonoids on histamine release induced by antigens. Among 21 compounds studied were the citrus flavonoids viz., hesperidin, naringin, tangeretin and nobiletin, Hesperidin, tangeretin and nobiletin. Exhibited slight to moderate activity, but naringin was not active. In a study of histamine release induced by tumor promoters, Middleton et al. (1987) found that quercetin, tangeretin and nobiletin all were effective. Matsuda (1991) in Japan, evaluated the primary orange juice flavonoid, hesperidin and found significantly ability to inhibit histamine release from pertinent mast cells of rats, suggesting that hesperidin may be an effective
component with anti-allergic action. It can be speculated that juice flavonoids may have anti-allergic activity through dietary intake, and at pharmacological doses may have substantial therapeutic effects. However, full clinical trials is required to confirm this hypothesis. In an other study, Manthey et al. (2000) reported that early indications from the work by Szent-Gyorgyi indicated that certain citrus flavonoids impacted the health of microvascular endothelial tissue. Subsequent research has validated these findings, and several study have shown that citrus flavonoids modulate inflammation by a number of mechanisms. Several of the main flavanone and flavone glycosides in citrus, and in particular, micronized diosmin and hesperidin, exhibit potent inhibition of inflammation in animals studies. In vivo administration of these compounds significantly inhibit prostaglandin production, as well as the biological actions of these pro-inflammatory mediators. Evidence suggests that much of this inhibition derives from the anti-oxidant properties of these citrus flavonoids or their metabolites. The other main class of citrus flavonoids, termed the polymethoxyflavones, has been recently shown to stimulate human monocytes. This inhibition is specific for TN/FA and two other cytokines, IL-10 and MIP-1. This specificity is paralleled by a known phosphodiesterase inhibition contribute to the mode of inhibition by the citrus polymethoxyflavones. In summary, the citrus flavonoids exhibit an array of anti-inflammatory effects, and thus may account for their beneficial effects on the micro vascular system.

b. Anti-cancer activity

Studies specifically on anti-cancer activity of flavonoids found in citrus juices have been reported worldwide. According to Marcel (1980) and Poste and Fidler (1980), the prognosis of cancer in man partially correlated with tumor growth, but was mainly determined by the invasiveness of the tumor and the metastatic capability of the tumor cell population. Growth of benign tumor leads to compression of surrounding tissues, but the tumor cell population does not invade these tissues and the prognosis after surgical removal of such tumors is excellent. However, malignant tumors not only grow, but also invade into surrounding normal tissues. During invasion, these tumors cross membranes, and as invasion proceeds, gain access to the circulatory system and are transported via lymph or blood vessels into distant organs. These secondary tumor deposits, called metastases or invasive tumors, lead to the further origin of tertiary tumor deposits causing the onset of an escalation, called the ‘metastatic cascade’, which makes the disease much less responsive to treatment and can lead to death of the patient.

Viadana et al. (1978) indicated that in almost all cases, spread is not directly from the primary cancer throughout the human body, but requires previous seeding or key disseminating organs namely from the lungs to the liver to the endocrine system and central nervous system. Primary gastrointestinal cancers, such as pancreatic, stomach, colon and rectal cancers disseminate to the liver, which in turn spread metastases throughout the body via the lungs. The currently used techniques of chemotherapy and irradiation attempt to slow the rate of growth and proliferation, but these treatments have serious side effects and title anti-invasive activity. However, means to study in vitro, and in some instances in vivo are now available and can generate data, which may lead to a better understanding of invasion mechanisms. In other study to evaluate citrus flavonoids for anti-invasive activity, the Florida Department of Citrus furnished samples of hesperidin, naringin, nobiletin and tangeretin to Bracke at Ghent in 1986 for screening. It was found (Bracke et al., 1989) that tangeretin was the
most potent of all citrus flavonoids tested for ability to inhibit the invasion of tumor cells into normal tissue fragments in organ culture. The consequences of this were immediately significant, as inhibition of cell invasion had hinder or prevent the 'metastatic cascade effect'. Bracke et al. (1991) carried out further research to test the possible anti-invasive activity in vivo, Bracke studied the distribution of tangeretin in body organs after oral and parenteral administration to laboratory mice. Which suggested that the effect of orally administered tangeretin be tested against invasion in the kidney and liver and the effects of intraperitoneal administration against lung metastasis.

Research has also shown that the citrus flavonoid tangeretin inhibits the invasion of tumor cells in organ culture and in the liver of syngeneic mice, Middleton (1991) investigated the effects of tangeretin and nobiletin, on the growth in vitro of a human squamous cell carcinoma line and stated that the citrus flavonoids markedly inhibited growth at all concentrations tested. Epidemiological studies have shown that consumption of citrus fruits can lower the risk of chronic disease including cancer and heart disease (Patil, 2000). In a study Manners et al. (2000) reported that limonoids are a group of complex triterpenoid compounds occurring only in plants of the Rutacea and Meliacea plant families, recognized to possess important biological activity and established to be the source of 'delayed bitterness' in citrus products. The similarity of chemical structural elements of the citrus as water soluble glucosides led to their evaluation as potential antitumor agents in mammalian systems. Test in mice have shown that citrus limonoids induce significant amounts of the chemical carcinogen detoxifying enzyme system glutathione-S-transferase in the liver and intestinal mucosa. In vitro tests with human breast cancer cells have shown the limonoids to have significant anti-tumor activity. However, there is need to have detail research to verify the chemopreventative efficacy of these compounds in humans and describe the potential limonoid reduce in citrus processing products and by-products.

Guthrie et al. (2000) reported that citrus juices have many components, which has shown the anti-cancer properties. The principle agents investigated were the citrus bioflavonoids and limonoids. The bioflavonoids, nobiletin, tangeretin, hesperetin and naringenin were found to be potent inhibitors of cellular proliferation in both estrogen receptor-positive (ER+) and negative (ER-) human breast cancer cell lines. In vivo experiments showed that animals given citrus juices developed fewer and smaller tumors than those given diets containing pure bioflavonoid or control diet. The greater inhibitory actions of the juices may be a result of the combined actions of their constituents flavonoids and limonoids, as well as other components such as vitamin C and hydroxy cinnamic acids. In comparison, the citrus limonoids viz. limonin, nomilin and a limonoid glucoside mixture were found even more potent inhibitors of ER-Cancer cell proliferation. The maximum tolerated dose, as a percentage of the diet, was found for each of the limonoids (Guthrie et al., 2000). The mechanism of action of both sets of compounds is yet to study. From histological analysis of mouse mammary tumours and cellular proliferation data, it appeared that increased cell death was occurring. FACS analysis was performed on cells treated with bioflavonoids and limonoids and found that tangeretin, hesperetin, and the limonoid glucoside mixture induced apoptosis in MDA-MB 435 ER-cells; whereas naringenin had no effect (Guthrie et al., 2000). In the late 1970s, Middleton has made major contributions to the study of anti-inflammatory, anti-allergy properties of flavonoids and in the mid 1980s, enlarged the
programme to include the study of anti-cancer and anti-viral properties. Bracke has recently discovered that the citrus flavonoid tangeretin has the ability to prevent invasion of normal tissue by cancer cells thus possibly of blocking the onset of the ‘metastatic cascade effect’, through which a primary cancerous tumor spreads to secondary and tertiary sites. During the 1960s and 1970s decades, it was found that citrus flavonoids affect capillary fragility, act as anti-platelet agents and may be important in preventing blood cell clumping which can lead to coronary thrombosis (Robbins, 1980).

c. Anti-viral activity
It has been known for over 40 years that certain natural flavonoids possess anti-viral activity. The presence of flavonoids in herbs and plant extracts is probably the basis for much of the use of these preparations in traditionally folk medicines. Vlietinck (1990) tested 6 flavonoids (hesperidin, naringin, nobiletin, tangeretin, heptamethoxy-flavone and tetra-O-methyl-scutellarein) all of which occur naturally in citrus juices, against herpes simplex type I and polio-myelitis viruses. Unfortunately, none of our citrus flavonoids have shown any promising anti-viral properties as yet, but research on the potential anti-viral activity of naturally occurring plant flavonoids has barely scratched the surface. It is possible that a compound with the proper structure activity relationship and pharmacokinetics properties exists in nature, which is a better anti-viral agent than synthetic drugs now used.

d. Effects on the circulatory system
The effect of flavonoids on bleeding and capillary fragility was first reported by Rusznyak and Szent-Gyorgi (1936), who used the term vitamin P to describe this phenomenon. However, due to the inconsistent action of bioflavonoid mixtures, the term vitamin P has fallen into disrepute by the 1950s. Robbins (1966) demonstrated that citrus bioflavonoids have an anti-adhesive effect on the clumping of red blood cells and blood platelets. Most significantly, Robbins (1974) reported that the methoxylated flavonoids were much more active than those with only hydroxyl groups. This offered an explanation for the variable activity of citrus bioflavonoid mixtures, as the quantities of methoxylated flavones in citrus, such as tangerine and nobiletin, are much less than the amounts of hydroxylated flavonoids such as hesperidin, the principle flavonoid in Szent-Gyorgyi’s vitamin P. Most recently, Robbins (1988) studies the effect of the grapefruit flavonoid naringin in lowering elevated hematocrits in human subjects. The results of this study indicated that a simple dietary procedure, including a grapefruit in the daily diet, can bring about beneficial changes.

Citrus beverages
Certain citrus beverages can influence the metabolism of some pharmacological agents, specifically those that are normally catabolized by certain cytochrome P450 isozymes. When these agents are administered along with grapefruit juice, their plasma concentration is significantly increased due to their decreased metabolism by cytochrome P450, with potentially harmful side effects (e.g., arrhythmias) (Spence 1997). Since this effect is observed after oral, but not, administration, citrus components are most likely having an effect on the intestinal and not the hepatic cytochrome P450 isozyme. Several citrus components, including flavones, flavonols, as well as non-flavonoid components have been shown to inhibit cytochrome P450 isozymes in vitro (Chan et al., 1998).

In conclusion, citrus fruit products and by product not only enhance the opportunity to establish processing industry in the country but also provide remuneration to the farmers for their produce during the glut in the market because of the utility of each tissue of fruit. On the other hand, days are not far away that
citrus could become an alternative of chemical medicine for numerous health problems on the dissemination of information available in the literature to human being.

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