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ABSTRACT

Citrus occupies a place of considerable importance in the fruit economy of the country. Citrus fruits are economically important with a large scale production of both the fresh fruit and processed products. Citiciculture as a garden industry existed for centuries in India. It comprises the third largest fruit industry. Among the Citrus fruits oranges contribute to roughly 80 percent of the world’s Citrus fruit production. There is strong, consistent evidence that a high intake of fruit and vegetables protects against various cancers. Citrus fruits are recognized as an important component of the human diet, providing a variety of constituents important to human nutrition, including vitamin C, folic acid, potassium, flavonoids, coumarins, pectin and dietary fibres. Citrus flavonoids have a broad spectrum of biological activities including antibacterial, antioxidant, antidiabetic, anticancer cardiovascular, analgesic, antiinflammatory, antiangiety etc. This report details the health benefits of Citrus, especially in cancer and the active components which are thought to produce these health benefits, their mechanisms of action and the level at which they are found in Citrus plants.

Keywords: Citrus, medicinal value, biological activity, Flavonoids.

INTRODUCTION

In the last two to three decades there has been a growing awareness of the role of diet in the etiology of the chronic diseases that are major contributors to morbidity and mortality in industrialized countries. Natural sources have provided us with an excellent hunting ground for discovering newer therapeutically active moieties and plant kingdom is one of these sources for giving us natural drugs. A wide range of bioactive substances have already been identified in foods and drinks and it is likely that many more exist. Many diseases, such as cancer, atherosclerosis and inflammation are caused by free radicals and lipid peroxidation inside human bodies. This kind of risk can be reduced by an appropriate dietary pattern including a great portion of fruit and vegetables because of the great amount of natural antioxidants in these plant foods. There are many biologically active substances in fruits including both nutrients and non-nutrients for which protective health effects have been postulated. Citrus fruits, including oranges, lemons, limes and grapefruits, are a principal source of such important nutrients, which are suggested to be responsible for the prevention of degenerative disease. These include vitamins C, folic acid, carotenoids, dietary fibres, potassium, selenium and a wide range of phytochemicals. A great number of epidemiological studies have shown that Citrus fruit consumption is protective in a variety of human cancers. It is presumed that most, if not all, of this protective effect is due to vitamin C. The frequency of Citrus fruit consumption is more closely related to risk reduction than vitamin C intake. This suggests that Citrus fruits contain not one but multiple cancer chemopreventive agents.

Citrus genus belongs to the large family Rutaceae, containing 130 genera in the seven subfamilies with many important fruit and essential oil producers. Classification

Kingdom - Plantae
Division - Magnoliophyta
Class - Magnoliopsida
Sub class - Rosidae
Order - Sapindales
Family - Rutaceae
Genus - Citrus

A genus of evergreen aromatic shrubs and small trees distributed in the Indo-Malaysian region, South-East Asia and China but cultivated throughout the topical and temperate region of the world. About 22 species occur in India, besides about 15 exotic species have been introduced for experimental trials. Citrus occupies a place of considerable importance in the fruit economy of the country. Citiciculture as a garden industry existed for centuries in India. It comprises the third largest fruit industry after mango and banana and occupies about 7.5% of land under fruits. Among the Citrus fruits of commerce oranges (sweet, mandarin and sour) are the most important as fresh fruit and they contribute to roughly 80 percent of the world’s Citrus fruit production. The species cultivated in India includes: Citrus
aurantifolia, C. aurantium, C. deliciosa, C. grandis, C. jambhiri, C. karna, C. latifolia, C. limetta, C. limettoides, C. limon, C. limonia, C. lycopersicaformis, C. macropera, C. maderaspatana, C. madurensis, C. medica, C. megaloxycarpa, C. nobilis, C. paradisi, C. paratangerina, C. pennivesiculata, C. pseudolimon, C. reshni, C. reticulata, C. rugulosa, C. sinensis, C. unshiu. Citrus is one of the most important fruits, which is consumed mostly fresh and has been used as an herbal medicine or additive or food supplement. Citrus fruit and juices have long been considered a valuable part of a healthy and nutritious diet and it is well established that some of the nutrients in Citrus promote health and provide protection against chronic disease. Citrus is believed to possess bioactivities such as antioxidant, anti-inflammatory, antimicrobial, and is suggested to be responsible for the prevention of cancer and degenerative diseases. Those bioactivities of Citrus are due to the presence of bioactive compound such as phenolics, flavonoids, essential oil and vitamins. The composition of the fruits is affected by climate, growing conditions, various treatments, maturity, rootstock and variety. The composition of some common Citrus fruits is given in table 1.

Citrus species are commonly known to contain flavonoids, coumarins and carotenoids. Some of which are isolated from common Citrus species and are summarized in Table 2.

PHARMACOLOGICAL ACTIVITIES RELATED TO DIFFERENT CHEMICAL CONSTITUENTS OF CITRUS

Citrus species show broad spectrum of pharmacological properties these properties are related to the presence of specific phytochemical groups.

Vitamin C

Citrus species are best known for being rich source of vitamin C. Vitamin C is an antiscorbutic factor and possess antioxidant properties.

Flavonoids

Citrus species are rich in flavonoids. Citrus flavonoids have antioxidant properties. They possess excellent hydroxyl radical scavenging activity and superoxide scavenging activity and antiliperoxidant activity.

Some health related properties of flavonoids, which are based on their anti-oxidant activity

a) Anti-carcinogenic properties

Plant flavonoids have attracted attention as important dietary cancer chemo protective agent. Citrus flavonoids possess anticarcinogenic and anti-tumor activities. Citrus flavonoids can inhibit the invasion of chick heart fragments and syngenic mice liver by malignant mouse tumour cells. Hesperidin and dioxim have exhibited anticarcinogenic activities in various in vivo studies. The polymethoxylated flavones have been shown in numerous in vitro studies to exert strong antiproliferative action against cancer cells and antigen activated T lymphocytes gastric cancer cells, prostate cancer cells squamous cell carcinoma and antimetastatic actions against human breast cancer cells have also been observed with tangeretin. Naringin, hesperidin, nobiletin and tangeritin inhibit the bacterial mutagenesis. Quercetin in experimental diets lowered the incidence of colon tumors in azoxymethanol treated rats and fibrosarcoma in mice. Naringin reduces lung metastasis in a breast cancer resection model.

Table 1: Chemical composition of Citrus Fruits (per 100g of edible portion)

<table>
<thead>
<tr>
<th></th>
<th>C. aurantifolia</th>
<th>C. aurantium</th>
<th>C. Limon</th>
<th>C. paradisi</th>
<th>C. reticulate</th>
<th>C. Sinensis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture, g</td>
<td>84.6</td>
<td>87.6</td>
<td>85.0</td>
<td>88.5</td>
<td>87.8</td>
<td>88.4</td>
</tr>
<tr>
<td>Protein, g</td>
<td>1.5</td>
<td>0.7</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Fat, g</td>
<td>1.0</td>
<td>0.2</td>
<td>0.9</td>
<td>0.1</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Fibre, g</td>
<td>1.3</td>
<td>0.3</td>
<td>1.7</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>10.9</td>
<td>10.9</td>
<td>11.1</td>
<td>10.0</td>
<td>10.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Minerals, g</td>
<td>0.7</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>90</td>
<td>26</td>
<td>70</td>
<td>30</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Phosphorous, mg</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.3</td>
<td>0.3</td>
<td>2.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Thiamine, mg</td>
<td>0.02</td>
<td>-</td>
<td>0.02</td>
<td>Juice 0.12</td>
<td>40*</td>
<td>-</td>
</tr>
<tr>
<td>Riboflavin, mg</td>
<td>0.03</td>
<td>-</td>
<td>0.01</td>
<td>Juice 0.02</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Niacin, mg</td>
<td>0.1</td>
<td>-</td>
<td>0.01</td>
<td>Juice 0.3</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>63</td>
<td>30</td>
<td>39</td>
<td>Juice -</td>
<td>68</td>
<td>50</td>
</tr>
<tr>
<td>Carotene, µg</td>
<td>15</td>
<td>1104</td>
<td>0</td>
<td>-</td>
<td>350*</td>
<td>0</td>
</tr>
<tr>
<td>Energy, K cal</td>
<td>59</td>
<td>48</td>
<td>57</td>
<td>45</td>
<td>-</td>
<td>43</td>
</tr>
</tbody>
</table>

* International Units
Table 2: Phytochemicals of some Citrus species

<table>
<thead>
<tr>
<th>Species</th>
<th>Flavonoids</th>
<th>Coumarins and psoralens</th>
<th>Carotenoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. sinensis</td>
<td>Hesperitin, naringin, tangeretin, naringenin, eriocitrin, hesperidin</td>
<td>Bergapten, bergamottin, bergaptolet, byakangelicin, citropten (limettin), imperatorin, isoimperatorin, isopimpinellin, phellopterin, prangol, scopoletin</td>
<td>Phytogene, phytofluene, β-carotene, cryptoxanthin, lutein, antheraxanthin, mutatoxanthins, recticulataxanthin, violaxanthin, luteoxanthins</td>
</tr>
<tr>
<td>C. bergamia</td>
<td>Naringin, neoeocitrin, hesperidin, neohesperidin, rhoifolin, tangeretin, nobiletin, rutin, aurinatanin</td>
<td>Aurapten, auraptenol, bergapten, bergapten, bergaptolet, byakangelicin, citropten, merarin, merarin, isomeranzin, osthol, seselin, scoparol, umbelliferone, xanthyletin</td>
<td>Phytogene, phytofluene, β-carotene, cryptoxanthin, lutein, antheraxanthin, mutatoxanthins, violaxanthin, luteoxanthins</td>
</tr>
<tr>
<td>C. reticulata</td>
<td>5-Hydroxy-7,8,3′,4′-tetramethoxyflavone</td>
<td>Bergapten, bergaptolet, bergamottin, citropten</td>
<td>Phytogene, phytofluene, β-carotene, cryptoxanthin, lutein, zeaxanthin, antheraxanthin, mutatoxanthins, violaxanthin, luteoxanthins</td>
</tr>
<tr>
<td>C. sinensis</td>
<td>Hesperidin, neohesperidin, xanthomircol, nobiletin, aurinatanin, ponkanetin</td>
<td>Aurapten, bergapten, bergaptolet, citropten, osthol, auroptolen</td>
<td>Phytogene, phytofluene, β-carotene, cryptoxanthin, lutein, antheraxanthin, mutatoxanthins, violaxanthin, luteoxanthins</td>
</tr>
<tr>
<td>C. sinensis</td>
<td>Rutin, limocitrin, sinensetin, isosinensetin, tangeretin, nobiletin, ponkanetin</td>
<td>Auraptenol, scoparol, xanthyletin</td>
<td>Phytogene, phytofluene, β-carotene, cryptoxanthin, lutein, antheraxanthin, mutatoxanthins, violaxanthin, luteoxanthins</td>
</tr>
<tr>
<td>C. limon</td>
<td>Naringin, eriocitrin, hesperidin, neohesperidin, nobiletin, apigenin, chrysoeriol, limocitrin, rutin, isorholofuran, neopiccin, nobiletin, limocitrin, isomericitrin, quercetin, isovitexin, phlorin, eryodictyol</td>
<td>Bergapten, bergamottin, byakangelicin, citropten, imperatorin, isoimperatorin, isopimpinellin, phellopterin, prangol, scoparol, scopoletin, umbelliferone, umbelliprenin, xanthyletin</td>
<td>Phytogene, β-carotene, cryptoxanthin, violaxanthin, auroxanthin</td>
</tr>
</tbody>
</table>

Table 3: Ancient and medieval uses of Citrus

<table>
<thead>
<tr>
<th>Species</th>
<th>Properties and uses in ancient and medieval sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrusaurantifolia</td>
<td>Fruit: antitoxic, appetizer and stomachic</td>
</tr>
<tr>
<td>Citruslimon</td>
<td>Fruit: digestive, remedy against plague Peal: antitoxic, appetizer, cardiac tonic, digestive, elixir, stomachic and pulmonary sedative. Pulp: anthelmintic, antipretic, appetizer, vascular stimulant, antiemetic, remedy against drunkenness, tonic, antitoxic, cures boils, throat and tonsils</td>
</tr>
<tr>
<td>Citrusaurantium</td>
<td>Flower: cardiac stimulant, digestive and stomachic, tonic Peal: digestive Pulp: in jaundice Wood: woodworm repellent</td>
</tr>
<tr>
<td>Citrus maxima</td>
<td>Pulp: antitoxic, appetizer, cardiac stimulant and stomach tonic</td>
</tr>
</tbody>
</table>

b) Cardiovascular properties

Several studies indicate that certain flavonoids may have a protective and therapeutic effect on coronary heart disease.

1. Effect on capillary fragility: The effect of flavonoids on bleeding and capillary fragility was reported by SzentGyorgyi in 1938, capillary damage can be treated with flavonoids. Diosmin produces a significant decrease in venous capacitance, venous distensibility and venous emptying time.

2. Effect of platelet aggregation: Citrus flavonoids show an antiadhesive and antiaggregation action against red cell clumping. Quercetin, fisetin, kaempferol and myricet inhibit platelet aggregation.

3. Effect on coronary heart disease: Flavonoids inhibits the oxidation of low density lipoprotein (LDL) and reduce thrombotic tendencies. Flavonoids reduce the rate of oxidized compound formation, thus inhibiting the growth of atherosclerotic complications.

4. Hypercholesterolemia: Dietary intake of orange juice or grape fruit juice reduces hypercholesterolemia.
Hesperidin and naringenin mixture lowered serum cholesterol level in rats and in ovariectomized mice. Tangeretin, nobiletin or polymethoxylated flavones significantly reduced serum triacylglycerols without altering HDL cholesterol level and without causing toxic effect.

5. Hypertension: Long term administration of hesperidin and glucosyl hesperidin brings about antihypertensive effect in hypertensive rats.

c) Hyperglycemia

*Citrus* flavonoids play important roles in preventing the progression of hyperglycemia, partly by binding to starch, increasing hepatic glycosylation and the glycogen concentration, and lowering hepatic gluconeogenesis. Hesperidin and naringin both significantly lowered the blood glucose level. Intravenous injection of diosmin reduced hyperglycemia induced by alloxan in rats.

d) Anti-inflammatory, Antiallergic and Analgesic activity

*Citrus* flavonoids like hesperidin, diosmin, quercetin and other flavonoids have shown dose dependent anti-inflammatory activity by influencing metabolism of arachidonincacid and histamine release. Diosmin reduced edema formation and inhibited the synthesis of prostaglandin E-2 (78.5%), prostaglandin F-2 (45.2%) and thromboxane B-2 (59.5%). Tangeretin and nobiletin exhibit slight to moderate activity. Hesperidin is an effective component with anti-allergic action. Hesperidin inhibits bone loss and decrease serum and hepatic lipids in ovariectomized mice. Citrusbergamia efficiently block the proinflammatory actions induced by IFN-γ and h on human keratinocytes. Naringenin may provide neuroprotection through suppression of pro-inflammatory pathways in activated BV-2 microglial cells.

e) Anti-microbial activity

One of the properties of flavonoids with their physiological action in the plants is their antifungal and antiviral activity. Quercetin and hesperitin actively inhibit the infectivity and/or replication of Herpes simplex virus, Polio viruses, Para influenza and Syncytial viruses. Naringin metabolites have antibacterial activity. Bergamot peel is a potential source of natural antimicrobials that are active against Gram-negative bacteria.

f) Anti-anxiety, antidepressant and antiallergic activity

Apigenin shows antidepressant activity; some flavonoids shows antiallergic, and antianxiety activity.

Ecological function

Some *Citrus* flavonoids can be used directly as repellents or toxins or used in the plant improvement programs to obtain more resistant crop. Rutin and isouqueritrin inhibit larval worm growth in the fruit and heart of the tobacco plant. With respect to mammals, tangeretin produces an increase in the neonatal death rates of rat and eupatoretin has a growing cytotoxic effect as the degree of hydroxylation and methylation. Eriodictyol, homoeriodictyol, luteolin and to a lesser extent vitexin and naringenin have a repellent effect.

OTHER PROPERTIES

Some *Citrus* flavonoids and their derivatives in the field of food technology are principally known for their ability to provide a bitter or sweet taste and as bitterness inhibitor. Naringin and neohesperidin convert into their corresponding flavones rhoifolin and neodiosmin leads to loss of bitterness. Some other *Citrus* flavonoids are although tasteless, can alter the taste of fruit juice and other food products. For example, the addition of the flavone neodiosmin to citrus juice can significantly reduce the threshold of the bitterness produced by limonin.

Limonoids

Limonoids are secondary metabolites in all *Citrus* fruits tissue and occur as either limonoliglucagones or limonoid glycosides. Limonoidaglycones, in particular limonin have been known and studied since the 1940’s in relation to the development of "delayed bitterness" in *Citrus* juices due to the hydrolysis of the corresponding glycosides. Limonoids exhibits a wide range of biological activities including insect antifeedent activity, antioxidant activity, antibacterial, antifungal, antiviral and cytotoxic activities. In vivo animal tests have been shown that *Citrus* limonoids induce glutathione S-transferase activity and inhibit fore stomach, oral, lung, skin and colon tumors in animals. In vitro studies with human breast cancer cells have been shown limonoids to be potent inhibitors of proliferation of estrogen receptor. Limonin could contribute to the cholesterol lowering effect of *Citrus* juice. Nomilin as an agent having anti-obesity and anti-hyperglycemic effects that are likely to be mediated through the activation of TGR5:limonin and nomilin in plant products is a significant indicator of the pest control. *Citrus* limonoids (limonin, nomilin and obacunone) which are obtained from seeds of *Citruslimon* showed antifeedent activity against *Spodopterafrugiperda* thus confirming their probable role as chemical defense agents in *Citrus*-herbivore interactions.

Coumarins

*Citrus*also contain bioactive compounds coumarins with potential health promoting properties. *Citrus* oils contain 5-methoxy psoralen (Bergapten). *Citrus* oils are the biggest contributors to furocoumarin content in fragranced products. UV irradiation is effective in activating essential oils and in particular bergapten. This photocotoxicity may be considered as a treatment option in some cases of lentigomaligna or lentigomaligna melanoma.
Some coumarins have been shown to possess following activities:

- Antimicrobial
- Antibacterial
- Antimutagenic
- Antiplatelet aggregating
- Antioxidant
- Anti inflammatory
- Anticarcinogenic
- Rodenticidal activity

CONCLUSION

Citrus plants are known to possess beneficial biological activities for human health. In addition, ethnopharmacological application of plants is a good tool to explore their bioactivities and active compounds. Citrus plants are easily available and show their effect in treatment of various diseases, so it is essential to give more research attention towards the safety and efficacy of this genus that will increase its utilization in therapeutic purpose to a more extent. Overall, the literature indicates a protective effect of Citrus against a number of chronic diseases and a specific role for Citrus fruits in some of these conditions related, in part, to their antioxidant capacity (from vitamin C, carotenoids, and certain phytochemicals) as well as their content of nutrients such as folate and potassium. This review chronicles the evolution of Citrus research from defining their participation as important contributor to improving human health and well-being. This report provides a comprehensive literature study on the health benefits of Citrus which describes and details how the various components of Citrus fruits and other parts can affect major causes of illness in community as well as approaches to increasing consumption in the community. Therefore, Citrus fruits could be categorized as functional foods containing components shown to have health promoting and anticancer activities. Bioactive components present in Citrus fruits that are implicated in degenerative disease prevention include vitamin C, β-carotene, flavonoids, coumarins, limonoids, folic acid and dietary fibres. This protective effect results from several biochemical properties of either individual or a combination of bioactive components of Citrus fruits including antioxidant activity.

REFERENCES


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