Review Article

# A Review on Citrus – "The Boon of Nature"

**Jaspreetkaur Sidana[1]*, Vipin Saini[1], Sumitra Dahiya[2], Parminder Nain[1], Suman Bala[1]**
[1]M.M. College of Pharmacy, MM University, Mullana (Ambala)-133207, India.
[2]Department of Pharmaceutical Science, G.J. University, Hissar (Haryana), India.
*Corresponding author's E-mail: preetisidana@gmail.com

**Accepted on:** 17-12-2012; **Finalized on:** 31-01-2013.

**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. Citriculture 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, antianxiety 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[1,2] because of the great amount of natural antioxidants in these plantfoods[3]. 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[4]. 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[5].

*Citrus* genus belongs to the large family Rutaceae, containing 130 genera in the seven subfamilies with many important fruit and essential oil producers[6].

Classification[7]

| | | |
|---|---|---|
| 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. Citriculture 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. limettioides, C. limon, C. limonia, C. lycopersicaeformis, C. macroptera, 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*[8]. *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[9]. 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[8-11].

## 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[13,14].

### Flavonoids

*Citrus*species are rich in flavonoids. *Citrus* flavonoids have antioxidant properties[15-17]. They possesses excellent hydroxyl radical scavenging activity[18-20] superoxide scavenging activity[21] and antilipoperoxidant activity[15,16].

### 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[22] *Citrus* flavonoids possess anticarcinogenic and anti-tumor activities.[23] *Citrus* flavonoids can inhibit the invasion of chick heart fragments and syngenic mice liver by malignant mouse tumour cells[24]. Hesperidin and diosmin have exhibited anticarcinogenic activities in various *in vivo* studies[25,26]. The polymethoxylated flavones have been shown in numerous *in vitro* studies to exert strong antiproliferative action against cancer cells[27-32] antigen activated T lymphocytes[33] gastric cancer cells[34], prostate cancer cells[35] squamous cell carcinoma[28] and antimetastatic actions against human breast cancer cells have also been observed with tangeretin[36]. Naringin, hesperidin, nobiletin and tangertin inhibit the bacterial mutagenesis[37]. Quercetin in experimental diets lowered the incidence of colon tumors in azoxymethanol treated rats[38] and fibrosarcoma in mice[39]. Naringenin reduces lung metastasis in a breast cancer resection model[40].

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

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

* International Units

**Table 2:** Phytochemicals of some *Citrus* species

| Species | Flavonoids | Coumarins and psoralens | Carotenoids |
|---|---|---|---|
| *C. aurantifolia* | Hesperitin, naringin, tangeretin, naringenin, erioctrin, hesperidin | Bergapten, bergamottin, beragaptol, byakangelicin, citropten (limettin), imperatorin, isoimperatorin, isopimpinellin, phellopterin, prangol, scopoletin | - |
| *C. aurantium* | Naringin, neoeriocitrin, hesperidin, neohesperidin, rhoifolin, tangeretin, nobiletin, rutin, auranetin | Aurapten, auraptenol, bergapten, meranzin, meranzin hydrate, isomeranzin, osthol, seselin, scoparon, umibelliferone, xanthyletin | - |
| *C. bergamia* | 5-Hydroxy-7,8,3',4'-tetramethoxyflavone | Bergapten, bergaptol, bergamottin, citropten | - |
| *C. paradise* | Naringin, kaempferol glycoside, isosakuranetin, hesperidin, poncirin, neohesperidin, rhoifolin, tangeretin, nobiletin | Aurapten, bergapten, bergamottin, bergaptol, byakangelicin, citropten, marmin, meranzin, isomeranzin, osthol, seselin, umbelliferone, xanthyletin | Phytoene, phytofluene, β-carotene, cryptoxanthin, lutein, antheraxanthin, mutatoxanthins, recticulataxanthin, violaxanthin, luteoxanthins |
| *C. reticulate* | Hesperidin, neohesperidin, xanthomicrol, nobiletin, auranetin, ponkanetin | Aurapten, bergapten, bergaptol, citropten, osthol, auroptenol | Phytoene, phytofluene, β-carotene, cryptoxanthin, lutein, zeaxanthin, antheraxanthin, mutatoxanthins, violaxanthin, luteoxanthins |
| *C. sinensis* | Rutin, limocitrin, sinensetin, isosinensetin, tangeretin, nobiletin, ponkanetin | Auraptenol, scoparon, xanthyletin | Phytoene, phytofluene, β -carotene, β -carotene, cryptoxanthin, lutein, antheraxanthin, mutatoxanthins, violaxanthin, luteoxanthins, auroxanthins |
| *C.limon* | *Naringin*, eriocitrin, hesperitin, *hesperidin*, neohesperidin, diosmin, apigenin, chrysoeriol, limocitrin, rutin, isorhoifolin, neoponcitrin, nobeletin, limocitrol, isolimocitrol, quercetin, isovitexin, phlorin, eryodictyol | Bergapten, bergamottin, byakangelicin, citropten, imperatorin, isoimperatorin, isopimpinellin, phellopterin, prangol, scoparon, scopoletin, umbelliferone, umbelliprenin, xanthyletin | Phytofluene, β-carotene, cryptoxanthin, violaxanthin, auroxanthin |

**Table 3:** Ancient and medieval uses of *Citrus*[12]

| Species | Properties and uses in ancient and medieval sources |
|---|---|
| *Citrusmedica* | Leaf: digestive, insect repellant.<br>Fruit: antiemetic, antitoxic remedy against plague, stomach tonic.<br>Peel: digestive, tonic, antitoxic, diuretic.<br>Pulp: pulmonary sedative, antiemetic, digestive, antitoxic |
| *Citrusauantiifolia* | Fruit: antitoxic, appetizer and stomachic |
| *Citruslimon* | Fruit: digestive, remedy against plague<br>Peel: antitoxic, appetizer, cardiac tonic, digestive, elixir, stomachic and pulmonary sedative.<br>Pulp: antihelmentic, antipyretic, appetizer, vascular stimulant, antiemetic, remedy against drunkness, tonic, antitoxic, cures boils, throat and tonsils |
| *Citrusaurantium* | Flower: cardiac stimulant, digestive and stomachic, tonic<br>Peel: digestive<br>Pulp: in jaundice<br>Wood: woodworm repellent |
| *Citrus maxima* | Pulp: antitoxic, appetizer, cardiac stimulant and stomach tonic |

### 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[41].
2. Effect of platelet aggregation: *Citrus* flavonoids show an antiadhesive and antiaggregation action against red cell clumping[42]. Quercetin, fisetin, kaempferol and myricet inhibit platelet aggregation[43].
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[22].
4. Hypercholesterolemia: Dietary intake of orange juice or grape fruit juice reduces hypercholesterolemia[44,45].

Hesperidin and naringenin mixture lowered serum cholesterol level in rats and in ovariectomized mice[46,47]. Tangeretin, nobiletin or polymethoxylated flavones significantly reduced serum triacylglycerols without altering HDL cholesterol level and without causing toxic effect[48].

5. Hypertension: Long term administration of hesperidin and glucosyl hesperidin brings about antihypertensive effect in hypertensive rats[49].

**c) Hyperglycemia**

*Citrus* flavonoids play important roles in preventing the progression of hyperglycemia, partly by binding to starch, increasing hepatic glycolysis and the glycogen concentration, and lowering hepatic gluconeogenesis[50]. Hesperidin and naringin both significantly lowered the blood glucose level[51]. Intravenous injection of diosmin reduced hyperglycemia induced by alloxan in rats[52].

**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 arachidonicacid and histamine release[53-56]. 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[57]. Hesperidin is an effective component with anti-allergic action[58]. Hesperidin inhibits bone loss and decrease serum and hepatic lipids in overiectomiced mice[47]. *Citrus*bergamia efficiently block the proinflammatory actions induced by IFN-γ and h on human keratinocytes[59]. Naringenin may provide neuroprotection through suppression of pro-inflammatory pathways in activated BV-2 microglial cells[60,61].

**e) Anti-microbial activity**

One of the properties of flavonoids with their physiological action in the plants is their antifungal and antiviral activity[62]. Quercetin and hesperitin actively inhibit the infectivity and/or replication of Herpes simplex virus, Polio viruses, Para influenza and Syncytial viruses[63]. Naringin metabolites have antibacterial activity[64]. Bergamot peel is a potential source of natural antimicrobials that are active against Gram-negative bacteria[65].

**f) Anti-anxiety, antidepressant and antiallergic activity**

Apigenin shows antidepressant activity[66] some flavonoids shows antiallergic,[67] and antianxiety activity[68].

**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[69]. Rutin and isoquercitrin inhibit larval worm growth in the fruit[70] and heart of the tobacco plant[71]. With respect to mammals, tangeretin produces an increase in the neonatal death rates of rat[72] and eupatoretrin has a growing cytotoxic effect as the degree of hydroxylation and methylation[73]. Eriodictoyl, homoeriodictyol, luteolin and to a lesser extent vitexin and naringenin have a repellent effect[74].

## 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[75]. 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 citric juice can significantly reduce the threshold of the bitterness produced by limonin[76].

**Limonoids**

Limonoids are secondary metabolites in all *Citrus* fruits tissue and occur as either limonoidaglycones or limonoid glycosides[77]. 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[78,79]. Limonoids exhibits a wide range of biological activities including insect antifeedent activity,[80] antioxidant activity[81-82] antibacterial, antifungal, antiviral and cytotoxic activities[83]. In vivo animal tests have been shown that *Citrus* limonoids induce glutathione S-transferase activity[84] and inhibit fore stomach, oral, lung, skin and colon tumors in animals.[85-86] *In vitro* studies with human breast cancer cells have been shown limonoids to be potent inhibitors of proliferation of estrogen receptor[87-89]. Limonin could contribute to the cholesterol lowering effect of *Citrus* juice[90]. Nomilin as an agent having anti-obesity and anti-hyperglycemic effects that are likely to be mediated through the activation of TGR5[91]limonin and nomilin in plant products is a significant indicator of the pest control[92]. *Citrus* limonoids (Limonin, nomilin and obacunone) which are obtained from seeds of *Citruslimon* showed antifeedent activity against *Spodopetrafrugiperda* thus confirming their probable role as chemical defense agents in *Citrus*-herbivore interactions[93].

**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[94]. UV irradiation is effective in activating essential oils and in particular bergapten. This phototoxicity may be considered as a treatment option in some cases of lentigomaligna or lentigomaligna melanoma[95].

Some coumarins have been shown to possess following activities:

- Antimicrobial[83], Antibacterial[96]
- Antimutagenic[97-98]
- Antiplatelet aggregating[99]
- Antioxidant[100-102]
- Anti inflammatory[103]
- Anticarcinogenic[104-105]
- Rodenticidal activity[106]

## 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 antioxidative 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


1. Ames B.N., Shigenaga M.K. and Hagen T.M., Oxidants, antioxidants, and the degenerative diseases of aging, Proceedings of the National Academy of Sciences of the United States of America, 90, 1993,7915-7922.
2. Weisburger J.H., Mechanisms of action of antioxidants as exemplified in vegetables, tomatoes and tea, Food Chemical Toxicol, 37, 1999, 943-948.
3. Cheung L.M., Cheung P.C.K. and Ooi V.E.C., Antioxidant activity and total phenolics of edible mushroom extracts,Food Chemistry, 81, 2003, 249-255.
4. Silalahi J., Anticancer and health protective properties of *Citrus* fruit components, Asia Pacific J ClinNutr ,11(1), 2002, 79–84
5. Miller E.G., Sanders A.P.G., Couvillon A.M., Binnie W.H., Hasegawa S,LamL.K.T.,*Citrus*Limonoids as Inhibitors of Oral Carcinogenesis, Food Technol,1994, 110–114.
6. Lucker J., Tamer M.K., Schwab W., Verstappen F.W.A., Plas L.H.W.V., Bouwmesster H.J., Verhoeven H.A, Monoterpene biosynthesis in lemon (*Citrus limon*). European Journal of Biochemistry, 269, 2002, 3160-3171.
7. http://en.wikipedia.org/wiki/lemon
8. Anonymous,The wealth of india. a dictionary for indian raw material and industrial products – raw materials (csir, new delhi), 3, 1992, pp. 609-678.
9. Karimi E., Oskoueian E., Hendra R., Oskoueian A., Jaafar H.Z.E.,Phenolic Compounds Characterization and Biological Activitiesof *Citrus aurantium*Bloom,Molecules,17,2012,1203-1218.
10. Kawaii S., Tomono Y., Katase E., Ogawa K., Yano M., Koizumi M., Chihiro I. and Furukawa H., Quantitative study of Flavonoids in leaves of *Citrus* plants, Journal of Agricultural and Food Chemistry ,48, 2000, 3865-3871.
11. Chatterjee A. and Pakrashi S.C, In: *The Treatise on Indian medicinal plants.* National Institute of Science Communication, 3, CSIR, New Delhi, 1997, p-96.
12. Arias B.A.,Laca R. L.,Pharmacological properties of *Citrus* and their ancient and medieval uses in the Mediterranean region, Journal of Ethnopharmacology, 97, 2005, 89-95.
13. Nagy S., Vitamin C Contents of *Citrus* fruits and their Products: A Review, Journal of Agricultural Food Chemistry, 28(1), 1980.
14. Yu J., Wang L., Walzem R.L., Miller E.G., Pike L.M. and Patil B.S., Antioxidant activity of *Citrus* limonoids, flavonoids, and coumarins. Journal of Agricultural and Food Chemistry,53, 2005, 2009-2014.
15. Wang PF, Zheng RL, Inhibitors of the autoxidation of linoleic acids flavonoids in micelles, Chemistry and Physics of lipids, 63,1992, 37-40.
16. Morel I., Lescoat G., Cogrel P, Sergent O., Pasdecoup N., Bcissot P., CillardP,Cillard J., Antioxidant and iron-chelating activities of the flavonoids catechin, quercetin and diosmetin on iron-loaded rat heptaocyte cultures, Biochemical Pharmacology, 1, 1993,13-19.
17. Salah N., Miller N.J., Paganga G., Tijburg L., Bolwell G.P., and Rice Evans, C, Polyphenolicflavonols as scavenger of aqueous phase radicals and as chain – breaking antioxidants. Archieves of Biochemistry and Biophysics, 2, 1995, 339-346.
18. Pincemail J., Deby C., Lion Y., Braguet P., Hans P., Drien K. and Goutier R. Role of flavonoids in lipoperoxidation and radicalarractions. In: *Flavonoids and Bioflavonoids,* Proceedings of the 7th Hungraian Bioflavonoid symposium, Hungary, Farkas, L., Gabor, M. and kallay, F. (eds.). Elsevier Science Publishers, New York, 1986, pp.423-436.
19. Cillard J. and Cillard P., Composes phenoliquesetradicauxlibres, S.T.P. Pharma, 4, 592-596.
20. Loizzo M.R., Tundis R., Bonesi M., Menichini F., De Luca D., Colica C., and Menichini F.,Evaluation of *Citrus* aurantifolia peel and leaves extracts for their chemical composition, antioxidant and anti-cholinesterase activities, J. Sci Food Agric, 92(15), 2012,2960-7.
21. Darmon N., Ferrandiz V., Canal M.T. and Mitjavilla S., Activite antiradicallire de flavonoides vis-à-vis de l'anion superoxide et du radical hydroxyle, Liaison-Grupe Polyphenols Bull., 15, 1990,158-162.
22. Hertog M.G.L., Feskeens E.J.M., Hollman C.H., Katan M.B. and Kromhout D, Dietary antioxidant flavonoids and risk of coronary heart disease, Lancet, 342, 1993,1007-1011.

23. Lee D. H., Park K. I., Park H. S., Kang S. R., Nagappan A., Kim J. A., Kim E. H., Lee W. S., Hah Y. S., Chung H. J., An S. J., Kim G. S, Flavonoids Isolated from Korea *Citrus aurantium* L. Induce G2/M Phase Arrest and Apoptosis in Human Gastric Cancer AGS, Evid based complement alternat med, 2012.

24. Bracke M.E., Vyncke B., Van Larebeke N.A., Bruyheel E.A., De Bruyne G.K., De Pestel G.H., De Caster W.J., Espeel M.F. and Mareel M., The flavonoid tangeretin inhibits invasion of MO4 mouse cells into embryonic chick heart in vitro, Clinical and Experimental Metastasis, 7,1989, 283-300.

25. Tanaka T., Makita H., Kawabata K., Mari H., Kakumoto M., Satoh K., Hara A., Sumida T., Fukutani K., Tanaka T. and Ogawa H., Chemoprevention of azoxymethane induced rat colon carcinogenesis by the naturally occurring flavonoids, diosmin and hesperidin. Carcinogenesis, 18, 1997, 957-965.

26. Yang M., Tanaka T., Hirose Y., Deguchi T., Mori H. and Kawada Y, Chemopreventive effects of diosmin and hesperidin on N-butyl-N-(4hydroxybutyl)-nitrosamine induced urinary bladder carcinogenesis in male ICR mice. International Journal of Cancer, 73, 1997, 719.

27. Kandaswami C., Perkins E., Soloniuk D.S., Drzewiecki G. and Middleton E, Antiproliferative effects of *Citrus* flavonoids on a human squamous cell carcinoma in vitro. Cancer Letter, 56,1991, 147-152.

28. Sugiyama S., Umehara, K., Kuroyanagi, M., Veno, A. and Taki, T., Studies on the differentiation inducers of myeloid leukemic cells from *Citrus* species. Chemical and Pharmaceutical Bulletin, 41, 1993,714-719.

29. Hirano T., Abe K., Gotoh M. and Oka K, *Citrus* flavone tangeretin inhibits leukemic HL-60 cell growth partially through induction of apoptosis with less cytotoxicity on normal lymphocytes. British Journal of Cancer, 72, 1995,1380-1388.

30. Mak, N.K., Wong-Leung, Y.L., Chan, S.C., Wen, J., Leung, K.N. and Fung, M.C, Isolation of antileukemia compounds from *Citrus reticulata*. Life Sciences, 58,1996, 1269.

31. Kawaii, S., Yomono, Y., Katase, E., Ogawa, K. and Yano, M, Antiproliferative activity of flavonoids on several cancer cell lines. Bioscience, Biotechnology and Biochemistry, 63,1999, 896-899.

32. Iwase, Y., Takemura, Y., Ju-ichi, M., Yano, M., Ito, C., Furujawa, H., Mukainaka, T., Kuchide, M., Tokuda, H. and Nishino, H, Cancer chemopreventive activity of 3, 5, 6, 7, 8, 3', 4'-heptamethoxyflavone from the peel of *Citrus* plants. Cancer Letter, 163,2001, 7-9.

33. Mookerjee, B.K., Lee, T.P., Lippes, H.A. and Middleton, E, Some effects of flavonoids on lymphocyte proliferative responses. Journal of Immunopharmacology, 8,1986, 371-392.

34. Scambia, G., Ranelletti, F.O., Benedetti-Panici, P., Piantelli, M., Bonanno, G., De Vincenzo, R., Ferrandian, G., Rumi, C., Larocca, L.M. and Mancuso, S., Inhibitory effect of quercetin on OVCA 433 cells and presence of type II oestrogen binding sites in primary ovariun tumors and cultured cells. British Journal of Cancer, 62, 1990, 942-946.

35. Peterson, G. and Barnes, S., Genistein and biochain inhibit the growth of human prostate cancer cells but not epidermal growth factor receptor tyrosine auto-phosphorylation. Prostate, 22, 1993, 335-345.

36. Bracke, M.E., Bruyneel, E.A., Vermeulen, S.J., Vennekens, K., Marck, V. and Mareel, M.M., *Citrus* flavonoid effect on tumor invasion and metastases. Food Technology, 48, 1994, 121-124.

37. Calomme, M., Pieters, L., Vlietinck, A. and Berghe, D.V., Inhibition of bacterial mutagenesis by *Citrus* flavonoids. PlantaMedica., 62, 1996, 222-226.

38. Deschner, E.E., Ruperto, J., Wong, G. and Newmark, H.L., The effect of dietary quercetin and rutin on AOM-induced acute colonic epithelial abnormalities in mice fed a high fat diet.Nutrition Cancer, 20, 1993,199-204.

39. Elangovan, V., Sekar, N. and Govindasamy, S., Chemopreventive potential of dietary bio-flavonoids against 20-methylcholanthrene induced tumorogenesis. Cancer Letter,87, 1994, 107-113.

40. Qin L., Jin L., Lu L., Lu X., Zhang C., Zhang F., Liang W, Naringenin reduces lung metastasis in a breast cancer resection model,.Protein Cell, 2(6), 2011, 507-16.

41. Geroulakos, G. and Nicolaides, A.N., Controlled studies of Daflon 500 mg in chronic venous insufficiency, Angiology, 45,1994, 549-553.

42. Robbins, R.C., Action of flavonoids on blood cells: Trimodal action of flavonoids elucidates their inconsistent physiologic effects, International Journal for Vitamin and Nutrition Research, 44,1974, 203-216.

43. Tzeng, S.H., Ko, W.C., Ko, F.N. and Teng, C.M, Inhibition of platelet aggregation by some flavonoids, Thrombosis Research, 64, 1991,91-100.

44. Kurowska, E.M., Borradaile, N.M., Spence, J.D. and Carroll, K.K. Hypocholesterolemic effects of dietary *Citrus* juices in rabbits, Nutrition Research, 20, 2000, 121-129.

45. Kurowska, E.M., Spence, J.D., Jordan, J., Wetmore, S., Freeman, D.J., Piche, L.A. and Serratore, P, HDL cholesterol raising effect of dietary orange juice in subjects with hypercholesterolemia, American Journal of Clinical Nutrition, 72, 2000, 1095-1100.

46. Bok, S.H., Lee, S.H., Park, Y.B., Bae, K.H., Son, K.H., Jeong, T.S. and Choi, M.S, Plasma and hepatic cholesterol and hepatic activities of 3-hydroxy-3-methyl-glutaryl-CoA reductase and acyl CoA: Cholesterol transferase are lower in rats fed *Citrus* peel extract or a mixture of *Citrus* bioflavonoids, Journal of Nutrition, 129, 1999, 1182-1185.

47. Chiba, H., Uehara, M., Wu, J., Wang, X., Masuyama, R., Suzuki, K., Kanazawa, K. and Ishimi, Y., Hesperidin, a *Citrus* flavonoid inhibits bone loss and decreases serum and hepatic lipids in ovariectomized mice, Journal of Nutrition,133, 2003, 1892-1897.

48. Kurowska, E.M. and Manthey, J.A, Hypolipidemic effects and absorption of *Citrus*polymethoxylated flavones in Hamsters with diet-induced Hypercholesterolemia. Journal of Agricultural and Food Chemistry, 52,2004, 2879-2886.

49. Ohtsuki, K., Abe, A., Mitsuzumi, H., Kondo, M., Uemura, K., Iwasaki, Y. and Kondo, Y., Effects of Long-term Administration of Hesperidin and Glucosyl hesperidin to spontaneously hypertensive rats. Journal of Nutritional Science and Vitaminology,48, 2002, 420-422.

50. Shen W, Xu Y, Lu Y H,Inhibitory effects of *Citrus* flavonoids on starch digestion and antihyperglycemic effects in HepG2 cells, J Agric Food Chem, 60(38), 2012, 9609-19.

51. Jung, U.J., Lee, M.K., Jeong, K.S. and Chol, M.S, The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic-glucose regulating enzymes in C57 BL/KsJ-db/db Mice. Journal of Nutrition,134, 2004, 2499-2503.

52. Jean, T. and Bodinier, M.C, Mediators involved in inflammation: Effects of Daflon 500 mg on their release. Anigiology, 45,1994, 554-559.

53. Middleton, E., Drzewiwcki, G. and Krishnarao, D., Quercetin: An inhibitor of antigen-induced human basophil histamine. Journal of Immunology, 127,1981, 546-550.

54. Huet, R., Constituents of *Citrus* fruits with pharmacodynamic effect: Citroflavonoids. Fruits, 37, 1982, 267-271. .

55. Galati, E.M., Monforte, M.T., Kirjavainen, S., Forestieri, A.M., Trovato, A. and Tripodo, M.M, Biological effects of hesperidin, a *Citrus* flavonoid (note I): Antiinflammatory and analgesic activity, Farmaco, 40, 1994,709-712.

56. Tordera, M., Ferrandiz, M.L. and Alcaraz, M.J, Influence of anti-inflammatory flavonoids on granulation and arachidonic acid release in rat neutrophills, ZeitschriftfuerNaturforschung, 46,1994, 235-240.

57. Middleton, E. and Drzewiwcki, G., Effects of flavonoids and transitional metal cations on antigen-induced histamine release from human basophils. Biochemical Pharmacology, 31,1982, 1449-1453.

58. Matsuda, H., Pharmacological study on *Citrus* fruits. II. Anti-allergic effects of fruits of *Citrusunshiu*Markovicj (2) on flavonoids components. YakugakuZasshi, 111, 1991, 193-198.

59. Graziano A.C., Cardile V, Crascì L, Caggia S, Dugo P, Bonina F, Panico A. Protective effects of an extract from *Citrus* bergamia against inflammatory injury in interferon-γ and histamine exposed human keratinocytes,.Life Science, 90 (25-26),2012,968-74

60. Park H.Y, Kim G.Y, Choi Y.H. Naringenin attenuates the release of pro-inflammatory mediators from lipopolysaccharide-stimulated BV2 microglia by inactivating nuclear factor-κB and inhibiting mitogen-activated protein kinases**,** Int J.mol med., 30(1) 2012, 204-10.

61. Golechha M, Chaudhry U, Bhatia J, Saluja D, Arya DS. Naringin protects against kainic acid-induced status epilepticus in rats: evidence for an antioxidant, anti-inflammatory and neuroprotectiveintervention,Biol pharm bull, 34(3), 2011, 360-5.

62. Huet, R., Constituents of *Citrus* fruits with pharmacodynamic effect: Citroflavonoids. Fruits, 37, 1982, 267-271.

63. Kaul, T. N., Middleton, E. and Ogra, P. L, Antiviral effects of flavonoids on human viruses, Journal of Medical Virology, 15, 1985, 71-79.

64. Céliz G, Daz M, Audisio M. C.,Antibacterial activity of naringin derivatives against pathogenic strains,J. Appl. Microbiol., 111(3),2011,731-8.

65. Mandalari G, Bennett R N, Bisignano G, Trombetta D, Saija A, Faulds C B, Gasson M J, Narbad A., Antimicrobial activity of flavonoids extracted from bergamot (*Citrus* bergamiaRisso) peel, a byproduct of the essential oil industry, J ApplMicrobiol. 103(6), 2007, 2056-64.

66. Yi LT, Li JM, Li YC, Pan Y, Xu Q, Kong LD,Antidepressant-like behavioral and neurochemical effects of the *Citrus*-associated chemical apigenin**,** Life science, 82(13-14), 2008, 741-51

67. Itoh K, Masuda M, Naruto S, Murata K, Matsuda H.Antiallergic activity of unripe *Citrus* hassaku fruits extract and its flavanone glycosides on chemical substance-induced dermatitis in mic, J. Nat. med., 63(4), 2009,443-50

68. Pultrini, A.M., Galindo, L.A. and Costa, M., Effects of the essential oil from *Citrus aurantium* L. in experimental anxiety models in mice, Life Sciences, 78, 2006,1720-1725.

69. Garcia, O.B., Castillio, J., Marin, F.R., Ortuno, Ano and Rio, J.A.D., Uses and properties of *Citrus* flavonoids, Journal of Agriculture and Food Chemistry, 45, 1997, 4505-4515.

70. Duffey, S. S. and Isman, M.B, Inhibition of insect larval growth by phenolics in glandular trichomes of tomato leaves, Experientia, 37, 1981, 574-576.

71. Elliger, C.A., Chan, B.C. and Waiss, A.C., Flavonoids as larval growth inhibitors. Structural factors governing toxicity, Naturwissenchafften, 67, 1980,358-360.

72. Stout, M.G., Reich, M. and Huffman, M.N., 4', 5, 6,7-oxygenated flavones and flavonones, Cancer Chemotherapy Reports, 36, 1964, 23-24.

73. Kupchan, S.M., Sigel, C.W., Knox, J.R. and Udayamurthy, M.D, Tumor inhibitors 36. Eupatin and eupatoretin, two cytotoxic flavonols from *Eupatorium semiserratum*, Journal of Organic Chemistry, 34, 1969, 1460-1463.

74. Dreyer, D.L. and Jones, K.C, Feeding deterrency of flavonoids and related phenolics toward, *Schizophisgraminum* and *Myzuzpersice*. Aphid feeding deterrents in wheat. Phytochemistry, 20, 1981, 2489-2493.

75. Horowitz, R. and Gentili, B., Taste and structure in phenolic glycosides, Journal of Agricultural and Food Chemistry, 17,1969, 696-700.

76. Guadagni, D.G., Maier, V.P. and Turnbaugh, J.G, Effect of neodiosmin on threshold and bitterness of limonin in water and orange juice, Journal of Food Science, 41, 1976, 681-684.

77. Fong, C.H., Hasegawa, S., Herman, Z. and Ou, P, Limonoidglucosides in commercial *Citrus* juices, Journal of Food Sciences, 54, 1990, 1505-1506.

78. Hasegawa, S., Berhow, M.A. and Manners, G.D, *Citrus* limonoid research: an overview. In: *Citrus Limonoids – Functional Chemicals in Agriculture and Foods*. Berhow, M.A., Hasegawa, S. and Manners, G.D. (eds.), Oxford University Press, Washington DC, 2000, pp.1-8.

79. Shaw, P.E., Baines, L., Milnes, B.A. and Agmon, G, Commercial debittering process to upgrade quality of *Citrus* juice products. In: *Citrus Limonoids – Functional Chemicals in Agriculture and Foods*. Berhow, M.A., Hasegawa, S. and Manners, G.D. (eds.), ACS Symposium Series 758, American Chemical Society, Washington DC, 2000, pp.120-131.

80. Champagne, D.E., Koul, O., Isman, M.B., Scudder, G.G.E. and Towers, G.H.N, Biological activity of limonoids from the Rutales, Phytochemistry, 31, 1992, 377-394.

81. Mandadi K.K., Jayaprakasha G.K., Bhat N.G., Patil BS. Red Mexican grapefruit: a novel source for bioactive limonoids and their antioxidant activity, Z Naturforch ,62(3-4), 2007,179-88.

82. Poulose S.M., Harris E.D., Patil B.S.,*Citrus* limonoids induce apoptosis in human neuroblastoma cells and have radical scavenging activity, J Nutr., 135(4), 2005, 870-7.

83. Nakatani, N., Tamada, Y. and Fuwa, H., 7-Geranyloxy coumarine from juice oil of *Citrus*hassaku and antimicrobial effects of related coumarins, Agricultural and Biological Chemistry, 51,1987, 419-423.

84. Lam, L.K.T. and Hasegawa, S, Inhibition of benzo[□] pyrene-induced forestomachneoplasia in mice by *Citrus*limonoids, Nutrition Cancer, 12,1989a, 43-47.

85. Tanaka, T., Kohno, H., Kawabata, K., Honko, S., Miyake, M. and Wada, K., *Citrus*limonoids, obacunone and limonin, inhibit the development of Precursor lesion, aberrant crypy foci for colon cancer in rats. In: *Citrus Limonoids: Functional Chemicals in Agriculture and Foods*. Berhow, M.A., Hasegawa, S. and Manners, G.D. (eds.), American Chemical Society, Washington DC, 2000, pp.145-163.

86. Tanaka, T., Maeda, M., Kohno, H., Murakami, M., Kagami, S., Miyake, M. and Wada, K, Inhibition of azomethan-induced colon carcinogenesis in male F344 rats by the *Citrus* Limonoidsobaxunone and limonin, Carcinogenesis, 22, 2001, 193-198.

87. Guthrie, N., Chambers, A.F. and Carroll, K.K, Inhibition of MDA-MB-435 estrogen receptor-negative human breast cancer cells by *Citrus*limonoids, Proceedings of the American Association for Cancer Research,38, 1997, 1113.

88. Kim J., Jayaprakasha G K, Patil B. S.**,** Limonoids and their anti-proliferative and anti-aromatase properties in human breast cancer cells, Food funct, 2012

89. Hamdan D., E.I-Readi M. Z., Tahrani A, Herrmann F., Kaufmann D., Farrag N., El-Shazly A, Wink M. Z., Secondary metabolites of ponderosa lemon (*Citrus*pyriformis) and their antioxidant, anti-inflammatory, and cytotoxic activities,Naturforch c, 66(7-8), 2011,385-93.

90. Kurowska, E.M., Banh, C., Hasegawa, S. and Manners, G.D., Regulation of apo B production in Hep G2 cells by *Citrus*limonoids. In: *Citrus Limonoids – Functional Chemicals in Agriculture and Foods*. Berhow, M.A., Hasegawa, S. and Manners, G.D. (eds.), American Chemical Society, Washington DC, 2000, pp.175-184.

91. Ono E, Inoue J, Hashidume T, Shimizu M, Sato R, Anti-obesity and anti-hyperglycemic effects of the dietary *Citrus* limonoidnomilin in mice fed a high-fat diet. BiochemBiophys Res Commun., 410(3), 2011, 677-81.

92. Hafeez F., Akram W., Shaalan E.A., Mosquito larvicidal activity of *Citrus*limonoids against Aedesalbopictus, Parasitol Res., 109(1), 2011, 221-9.

93. Ruberto, G., Renda, A., Tringali, C., Napoli, E.M. and Simmonda, M.S.J, *Citrus* limonoids and their semisynthetic derivatives as antifeedent agents against *Spodapterafrugiperda* Larvae. A structure activity relationship study, Journal of Agricultural and Food Chemistry, 50, 2002, 6766-6774.

94. Lawrence, B.M., Progress in essential oils-coumarins and psoralens in *Citrus* oils. Perfume Flavor, 7, 1982, 57-65.

95. Menichini F., Tundis R., Loizzo M.R., Bonesi M., Provenzano E., de Cindio B, Menichini F.,In vitro photo-induced cytotoxic activity of *Citrus* bergamia and C. medica L., Diamante peel essential oils and identified active coumarins, Pharm boil, 48(9), 2010,1059-65

96. Melliou E., Magiatis P., Mitaku S., Skaltsounis A.L., Chinou E., Chinou I., Natural and synthetic 2,2-dimethylpyranocoumarins with antibacterial activity, J Nat prod, 68(1), 2005, 78-82.

97. Edenharder, R., Speth, C., Decker, M., Kolodziej, H., Kayser, O. and Platt, K.L, Inhibition of mutagenesis of 2-amino-methylimidazo [4,5-F] quinoline (IQ) by coumarins and furanocoumarins, chromoanoes and furanochromanones, Mutation Research, 345, 1995, 57-71.

98. Miyake, Y., Murakami, A., Sugiyama, Y., Isobe, M., Koshimizu, K. and Ohigashi, H, Identification of coumarins from lemon fruit (*Citrus limon*) as inhibitors of in vitro tumor promotion and superoxide and nitric oxide generation, Journal of Agricultural and Food Chemistry, 47, 1999, 3151-3157.

99. Chen, I.S., Lin, Y.C., Tsai, I.L., Teng, C.M., Ko, F.N., Ishikawa, T. and Ishi, H, Coumarin and anti-platelet aggregation constituents from *Zanthoxylumschinifolium*, Phytochemistry, 39, 1995,1091-1097.

100. Ng, T.B., Liu, F. and Wang, Z.T, Antioxidative activity of natural products from plants, Life Sciences, 66,2000, 709-723.

101. Fernandez, P.B., Barroso, I., Iglesias, I., Benedi, J. and Villar, A., Antioxidant activity of Fraxetin: in vivo and ex vivo parameters in normal situation versus induced stress, Biological and Pharmaceutical Bulletin, 24, 2001, 777-784.

102. Girennavar B., Jayaprakasha G.K., Jadegoud Y, NaganaGowda GA, Patil BS, Radical scavenging and cytochrome P450 3A4 inhibitory activity of bergaptol and geranylcoumarin from grapefruit, Bioorg Med Chem. , 15(11), 2007, 3684-91.

103. Sood S., Muthuraman A., Gill N.S., Bali M, Sharma P.D., Role of 7,8-dimethoxycoumarin in anti-secretary and anti-inflammatory action on pyloric ligation-induced gastritis in rats, J Asian Nat Prod Res., 12(7), 2010, 593-9.

104. Srimanth, K., Rao, V.R. and Krishna, D.R, Synthesis and evaluation of anticancer activity of some imidazothiazolyl, imidazobenzathiazolyl and dihydro-imidazothiazolylcoumarins, Drug Research, 52, 2002, 388-392.

105. Ito C, Itoigawa M, Ju-ichi M, Sakamoto N, Tokuda H, Nishino H, Furukawa H, Antitumor promoting activity of Coumarins from *Citrus* plants, Planta Med, 71(1), 2005, 84-7

106. El-Naggar M.E., Mikhail M.W., Rodenticidal activity of two natural coumarines from ether extract of *Citrus* bergamia, J Egypt SocParasitol. , 29(1), 1999, 75-84.

**Source of Support:** Nil, **Conflict of Interest:** None.