CITRUS WASTE REUSE FOR HEALTH BENEFITS AND PHARMA-/NEUTRACEUTICAL APPLICATIONS

Neelima Mahato, Kavita Sharma, Fatema Nabybaccus & Moo Hwan Cho
School of Chemical Engineering, Yeungnam University, Gyeongsan-si Gyongsanbuk-do, Republic of South Korea- 712 749

ABSTRACT

Citrus are the largest fruit crops grown across the globe. It is one of the most profitable crops in terms of economy as well as popular for nutritional benefits. The most interesting aspect about citrus is the availability of several varieties with attractive colours. Approximately 50 % of citrus remains unconsumed after processing as pith residue, peels and seeds. Direct disposal of these wastes cause serious environmental problems in terms of killing natural flora in the soil because of antibacterial properties of limonene oils. Seepage to underground waters or open water bodies affects water quality and aquatic life, respectively. Citrus waste reuse to obtain value added-phytochemicals and pectin is one of the popular topics in industrial research, food and synthetic chemistry. The present article reviews recent advances in exploring the effects of phytochemical compounds obtained from citrus wastes in view of various health aspects.

Address for correspondence
Neelima Mahato
School of Chemical Engineering
Yeungnam University, Gyeongsan-Si,
Gyeongsanbuk-do,
Republic of Korea- 712 749
Ph: +82-010-2798-8476
Email:neelapchem@gmail.com

Key words: Citrus waste, Phytochemical compounds, Hesperidin, Naringenin, Flavonoids, Polyphenols

INTRODUCTION

Citrus fruits have long been known for health benefits due to their nutrient contents and secondary metabolites, such as ascorbic acid, citric acid, phenolics, flavanoids, pectin, etc. Ascorbic acid helps in promoting the healing of mucosal lining by stimulating procollagen formation and subsequent synthesis of the same. (1) Various parts of the citrus fruits have been in popular use in traditional Indian and oriental medicines. Ripe fruits are good source of Vitamin-C, Vitamin-B complex and have curative properties for sore throat, cough, asthma, thirst, hiccough, earache, nausea and vomiting. These are also potent anti-scorbutic, stomachic tonic, stimulant expellant of poison, correct fetid breath and analgesic. Distilled water extract of the fruit is sedative and fruit and seed extracts are useful in palpitation and making cardiac tonics.(2-4)

Citrus belongs to family Rutaceae comprising 140 genera and 1300 species. It is one of the major fruit crop grown in tropical and subtropical regions. The main varieties are sweet oranges (Citrus sinensis), tangerine or mandarin (Citrus reticulata), grapefruit (Citrus vitis), lime (Citrus aurentifolia), and lemon (Citrus limonum). The major types of citrus fruits popularly grown are shown in Figure 1. Annual citrus production worldwide currently amounts over 70 million tons in approximately 140 citrus producing countries.(5) Out of the total citrus production, approximately 40-50 % is utilized in processing and manufacturing commercial products,

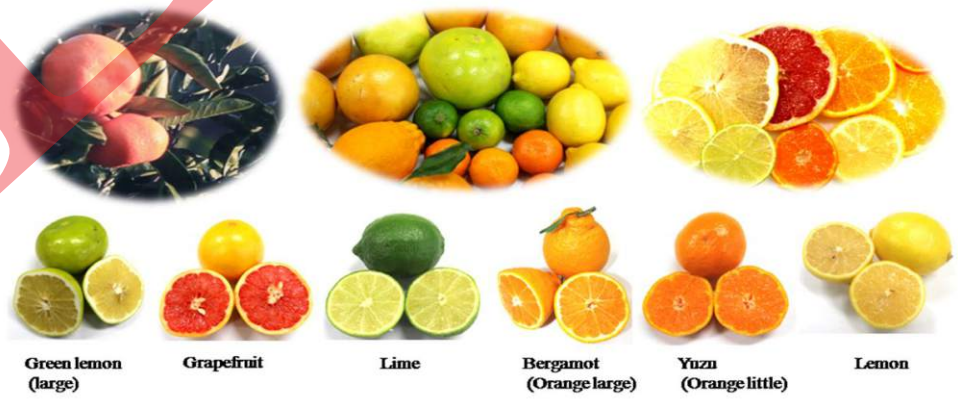

Figure 1. Main varieties of citrus fruits grown across the globe.

such as juice, jams, marmalades, jellies, flavouring agents, beverages and health drinks, etc.

CITRUS WASTES, ENVIRONMENTAL PROBLEMS AND REUSE

Citrus processing industries produce approximately 40 million tons of waste worldwide. The amount of residues obtained from citrus fruits constitutes almost 50 % of the original fruit mass. Citrus fruits contain ~ 40-55 % peels, ~30-35 % internal tissues and ~10 % seeds depending upon species, variety and climatic conditions where it is cultivated. The residue waste contain high amount of soluble sugars which make them highly perishable. Also, sugars and moisture facilitate high rates of fermentation. High content of organic matter especially peel oils (limonene) which carry antibacterial properties, make the citrus wastes inappropriate for direct disposals to landfills or dumping underground. Such disposals have been found to affect the natural and beneficial flora present in soil and aquatic bodies nearby. Furthermore, the oils tend to float on the surface of water bodies and limit the passage of oxygen from dissolving into the water affecting aquatic life. Also, citrus wastes are very difficult to dry by common conventional methods because of high moisture content.

Hence, extraction of oils, by-products and valuable phytochemical compounds from citrus wastes is not only a profitable alternative, but also a creative method of pollution abatement. Apart from essential oils (d-limonene), phenolics (coumarin, phenolic acid, phloroglucinol), flavanoids (hesperidin, naringenin, neo-hesperidin), carotenoids (lutein, β-carotene, lycopene, zeaxanthin), limonoids (limonin, normilin, limonoic acid), enzymes (pectinesterase, phosphatase, peroxidase), organic acids (citric acid, maleic acid, succinic acid), vitamins (Ascorbic acid, niacin, riboflavin), carbohydrates and pectins can be commercially extracted from the citrus wastes. (5) Some of the products created from citrus wastes are shown in Figure 2 and a collection of commercial brands are collaged in Figure 3. Commercial techniques and details of extraction processes are described in Reference. (5)

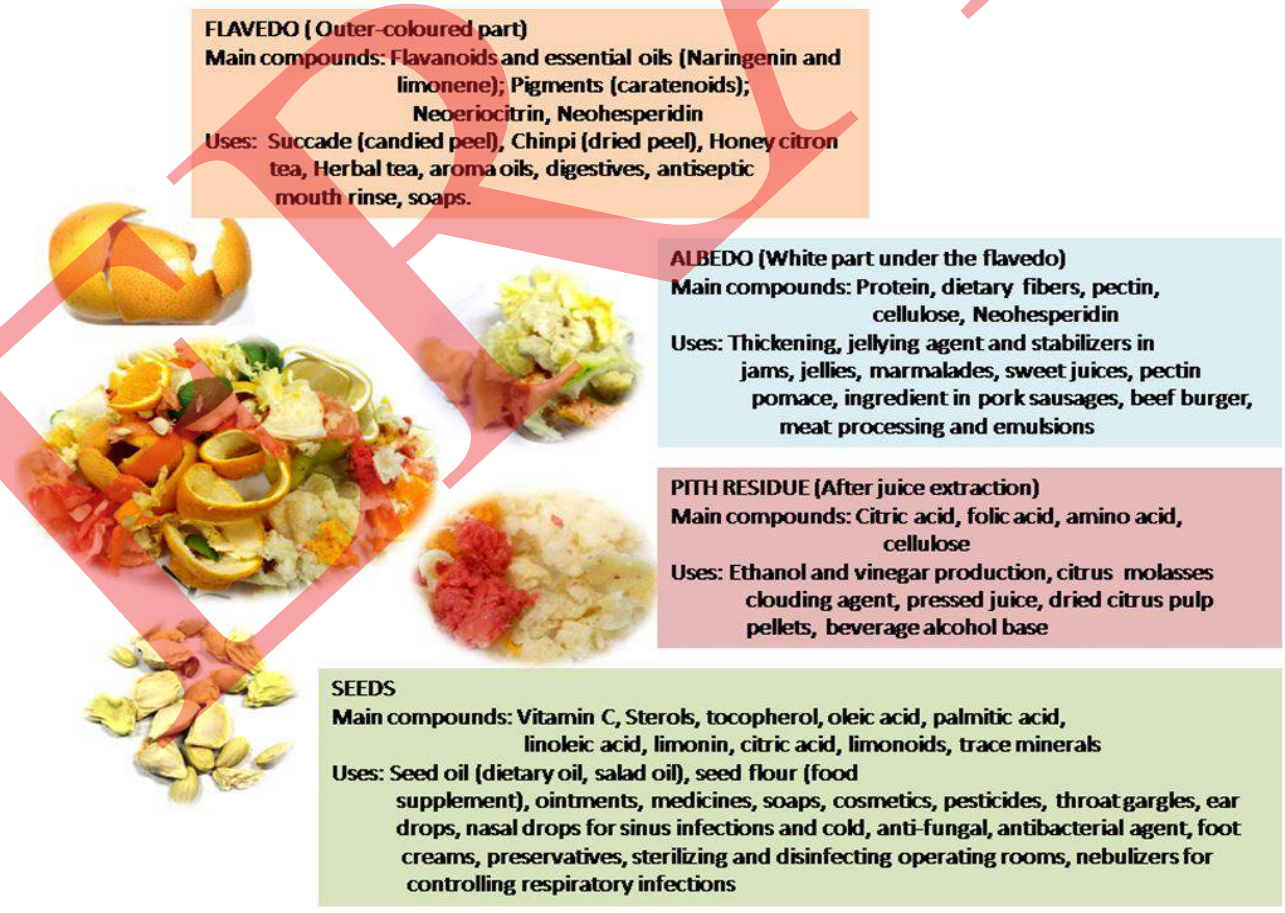

Figure 2. Main compounds and potential usage of different parts of citrus waste.

Commercial products from Citrus Albedo

Commercial products from Citrus Pith Residue

Commercial products from dried Citrus Peel

Cosmetics, skin care products and toiletries from Citrys Essential oils

Commercial products from Citrus Seeds

Figure 3. Commercial products created from citrus wastes (pulp residue, pith, peels and seeds). The photographs of the products are taken from a local supermarket in Gyeongsan city, South Korea.

*Disclaimer: Pictures of commercial products used in this article are purely for academic purpose and not meant for any advertisement or commercial benefit.

CITRUS WASTE DERIVED PHYTOCHEMICALS FOR HUMAN HEALTH

The phytochemicals and value added compounds extracted from citrus wastes are utilized in designing healthy foods, nutrient supplements, flavouring agents in foods processing, preservatives, health and power drinks in view of enhancing the quality of taste, aroma and curing deficiencies as well as restoring health. Citrus extracts are also utilized in cosmetic formulations for skin, hair and nails, antifungal and antibacterial lotions, soaps, perfumes and toiletries.

Obesity, hypertension, diabetes, heart diseases, cancer, memory loss, anxiety, etc., are closely related to personal lifestyle as well as food and dietary habits. Since last few decades, emphasis on the philosophy of "Prevention is better than cure" has gained huge attention and popularity in the mind-sets of common people and instigated awareness for achieving fitness

and good health. In this direction, nutrition and food scientists, dieticians and specialists have continuously researched along with medical practitioners and educationists on functional foods and nutritional supplements that can reduce the risk of diet related disorders/ diseases. Foods containing antioxidants and other phyto-nutrients, such as fruits and vegetables have proven to provide protective effects against many diseases especially degenerative processes caused by oxidative stress.(6-8) Obesity is an outcome of faulty life style, energy imbalance and abnormal metabolism. It is considered as a serious global health risk by World Health Organization (WHO). Obesity further increases the risk of dyslipidemia, hypertension, fatty liver disease, diabetes mellitus, cancers, osteoarthritis and asthma.(9, 10) As per WHO 2014 reports there are more than 1.9 billion adults of age 18 years and above identified as overweight and out of this, over 600 million were declared obese. Approximately 41 million children under the age of 5 were either overweight or obese. Overall, ~ 13 % of the world's population (11 % of men and 15 % of women) were obese in 2014. The world prevalence of obesity is continuously increasing and has become doubled between 1980 and 2014. Surprisingly, overweight and obesity are linked to more number of deaths worldwide then underweight (11). Furthermore, WHO predicted that by the year 2030, the affected population might increase to 3.3 billion (i.e., 1.7 times). This not only is expected to alter the quality of health and life, but also increases economic burden in terms of direct and indirect health care costs which includes health monitoring, nutritional supplements and surgical management.

Orlistat (Xenical) approved by FDA is a very popular and relatively effective drug of the present time and prescribed for long term treatment of obesity. It efficiently inhibits the pancreatic lipase enzyme and prevents the absorption of dietary fats. (12, 13) However, it also causes severe gastrointestinal side-effects. The side-effects make pharmacological approaches less attractive than therapeutic agents, which make natural remedies derived from phytochemicals a relatively more viable alternative. Therefore, the recent studies are being focused on searching innoxious and therapeutic natural products. In this regard, traditionally popular oriental herbal medicines, such as Diospyros kaki Thumb. and Citrus unshiu S. Marcov. Peels for treating obesity are being thoroughly investigated for developing potentially useful medicines/formulations. Both are popular as obesity curing herbal medicines in oriental countries, especially China, Korea and Japan. These fruits contain several bioactive compounds including polyphenols (esp. tannins), caratenoids, flavanoids, vitamins, minerals and dietary fibres. Polymethoxyflavones, hydroxyl polymethoxyflavones and hydroxylated polymethoxychalcones from Citrus sinensis has been reported to exhibit anticancer and antioxidant activities. (14)

Polyphenols present in Citrus limetta peels have shown to influence carbohydrate metabolism by inhibiting the α- glucosidase and α-amylase enzymes responsible for carbohydrate digestion. It also helps in avoiding chronic hyperglycemia that characterize type 2 Diabetes mellitus.(15) Citrus extracts especially flavanones and polymethoxyflavone have been found to provide estrogen effects and therefore, useful in hormone replacement therapy. The latter is a common therapy for estrogen deficiency in women especially post menopause which may lead further complications of osteoporosis, coronary diseases and bone density reduction , disturbed blood cholesterol profile and unpleasant symptoms, such as hot flashes and insomnia. Conventional pharmacological treatments have shown increased risks of cardiovascular diseases and induce breast cancer development, stroke and blood clots. (16)

Macromolecules present in our body fluid play important role in crystal aggregation, especially calcium oxalate crystallization leading to stone formation or urolithiasis. Calcium oxalate crystals are sparingly soluble or insoluble and tend to grow in size blocking urinary functions. In severe consequences, it leads to kidney failure and gall bladder malfunctioning. Even after treatment or removal of these stones, chances of reoccurrences are many and a big challenge for medical experts.

Table 1. Effect of citrus waste derived phytochemical compounds on various health aspects.

Citrus fruit	Fruit part extract	Active compound(s)	Effect on health	Animal Model	Ref.
Citrus unshiu	Water extract of dried peels (Chinpi)	Hesperidin, narirutin	Anti-aging effect	*In vivo* (Mice)	(17)

Table 1. Effect of citrus waste derived phytochemical compounds on various health aspects.(cont..)

Citrus sinensis (L.) Osbek	Water extract of dried peels	flavoniods, polymethoxyflavonoids	Hepatoprotective and immunosuppressive effects	*In vivo* (Mice)	(18)
Citrus sinensis	Peel extract in ethanol and water (hot and cold)	Tannins, saponins, phenolic compounds, essential oils and flavonoids	Antimicrobial effect against dental caries bacteria *Streptococcus mutans* and *Lactobaccillus* acidophilus	*In vitro* (agar well diffusion method)	(19)
Lemon peel	Antibacterial compounds isolated from methanolic extract using water, ethanol and n-hexane	8-geranyloxypsolaren; 8-geranyloxypsolaren; 5-geranyloxy-7-methoxycoumarin; Phloroglucinol 1-β-D glucopyranoside (phlorin)	Antimicrobial effect against dental caries bacteria, viz., *Streptococcus mutans* ATCC7270, *Prevotella intermedia, Porphyromonas gingivalis* 381	*In vitro*	*(20)*
Syrian *Citrus limon* L.	Peel extract from hydrodistillation of 3h	limonene, γ-terpinene, β-pinene, O-cymene and citral	Cytotoxic effect on colorectal carcinoma cells	*In vitro*	*(21)*
Citrus grandis L. Osbek	Peel extract in 80 % ethanol by Soxhlet, 8h	Flavonoids-naringin, narirutin, neohesperidin	Cardioprotective activity against cyclophosphamide (CYP) and doxorubicin (DOX) induced cardiac toxicity in rats	*In vivo* (Adult male Wistar rats)	*(22)*
Citrus paradisi (grapefruit)	Grapefruit Seed Extract (GSE) in 100 % ethanol	Flavonoids (naringin), Vit-C, Vit-E	Ameliorating effect on DOX-induced cardiomyopathy	*In vivo* (Adult male Sprague-Dawley rats)	*(23)*
Citrus spherocarpa (Korean hallabong)	Peel extract in water and ethanol followed by Sephadex G-75 gel filtration	HBE polysaccharides (HBE-I, II, III, IV)	*I*nhibitory effect on breast cancer metastasis	*In-vitro*	*(24)*
Citrus unshiu	Dried peel extract in 70 % ethanol, refluxed for 3h at 80°C; concentrated and lyophilize	Flavonoids (naringin, hesperidin)	Hepatoprotective effects; Improves lipid and bone metabolism	*In vivo* (Ovariectomized (OVX) rats (animal model of post menopausal osteoporosis)	*(25)*
Citrus reticulata	Peel extract in 70 % ethanol, by maceration for 5 days; filtration and evaporation	Flavanone and polymethoxyflavone	Modulation of blood cholesterol and bone density	*In vivo* (Ovariectomized (OVX) rats)	*(26)*

Table 1. Effect of citrus waste derived phytochemical compounds on various health aspects.(cont..)

Citrus karna	Peel extract by maceration in hexane, CHCl3, ethyl acetate and methanol, 24h	Flavonoids and phenolic acids	Anti-ulcerogenic and antioxidant activity	*In vivo* (Wistar rats; Water immersion (WIS) and Hypothermic restraint (HRS) stress models)	(27)
Citrus medica Linn.	Whole fruit aqueous extract by maceration	Flavonoids and phenolic acids	Antiulcer activity	*In vivo* (Mice)	(4)
Citrus auranthium	Flesh and peel extract in acetone, ethanol and methanol for 72h at 25 °C; filtered, evaporated and redissolved in DMSO (dimethyl sulphoxide) to a concentration of 50 mg/ml	Total phenolic content	Antioxidant activity:	*In-vitro* experiments on HepG2 (ATCC 8065) cells; Antioxidant activity by DPPH method	(8)
Citrus limetta	Aqueous peel extract	Polyphenolic compounds	Anti diabetic (antihyperglycemic); antioxidant activity	*In-vitro* (Antioxidant activity by DPPH method)	(28)
Citrus unshiu	Citrus Peel + *Diospyros kaki* fruit extract in boiling water, 2h; enzyme decomposition, 15g; enzyme viscozyme inactivation at 90 °C, 30 min; filtration and concentrated; sterlization	Polyphenolic (especially tannins) carotenoids, falvanoids, vitamins, minerals and dietary fibers	Anti-obesity effect	*In-vivo* (Mice)	(29)
Citrus sinensis; Citrus limon	Soxhlet extraction of citrus peel in ethyl acetate, acetone, ethanol, ether and water	Flavonoids, saponins, steroids, terpenoids, tannins, alkaloids	Antibacterial effect	*In-vitro* (Mice)	(30)

Table 1. Effect of citrus waste derived phytochemical compounds on various health aspects.(cont..)

Citrus aurentifolia	Peel extract in methanol fractioned using ethyl acetate, butanol and aqueous methanol	Tannins, alkaloids and polyphenols	Anti-helminthic effect against Heligmosomoides bakeri (nematod) in mice	*In vivo* (Mice)	(31)
Orange, lemon and mandarin	Ethanolic extract of citrus peel suspended in 0.5% DMSO	Limonene (90%), β-pinene (0.5%), α-pinene (0.5%), sabinene (0.3%)	Antihelminthic effect on Ascaridia galli in chickens collected from their intestines	*In vivo* (Chicken)	(32)
Citrus limon	Peel essential oils from cold pressing	terpenoids	Antifungal effect on oral candidiasis (*Candida albicans*) fungus	*In-vitro*	(33)
Citrus	Extract of multiple varieties of citrus peels (Gold Lotion or GL copmrising extracts from the peels of six citrus fruits produced in Japan)	flavonoida, polymethoxyflavones (PMFs)	Anticancer activity (Skin, Colon, Prostate)	*In-vivo* (Female ICR mice)	(34)
Citrus sinensis L.	Essential oil from hydrodistillation	α-terpineol (33.59%), γ-muurolene (4.44%), D-limonene (17.74%), linalool (9.73%), citronellol (4.88%), and isopiperitenone (3.58%), etc.	Antituberculosis effect	*In-vitro*	(35)
Citrus kiyomi x *ponkan;* GKP (jeju Hallabong tangor)	Glycosides of GKP converted into aglycosides by enzyme cytolase	decreased amount of flavanone rutinoside forms (nerirutin and hesperidin) and increased amount of flavanone aglycoside forms (naringenin and hesperetin)	Antioxidant and anti-inflamatory activity	*In-vitro* (RAW 264.7 cells)	(36)
Citrus unshiu	Peel waste is lyophilized, ground and suspended in 50 mM sodium acetate buffer	Hesperidin and narirutin	Proangiogenic effects; improves blood circulation	*In-vitro* (Human umbilical vein endothelial cells-HUVECs)	(35)
Citrus	Extracted and purified	Bioflavonoid naringenin	Cholesterol regulation	*In vivo* (Rats)	(37)
Citrus	Extracted and purified	Bioflavonoid naringenin	Hepatic cholesterol regulation	*In vivo* (Spragne Dawley rats)	(38)

Table 1. Effect of citrus waste derived phytochemical compounds on various health aspects.(cont..)

Orange	Peel and pulp residue, shredded, dried and added to cattle feed	Essential oils	Antimicrobial activity	*In vitro* (Cattle)	(39)
Citrus reticulata	Peel extract in ethanol from soxhlation and maceration	phenolics and flavonoids	Anti-aging effect	*In vitro* (Antioxidant and anti-enzyme assay)	(40)
Citrus	Peel extract and formulations	bioflavonoids	Inhibition of stone forming proteins	*In vivo* (Rats)	(41)
Citrus kawachiensis	Dried peel powder	Auraptene	Anti-inflamatory effect	*In vivo* (Mice)	(42)
Citrus reticulate, Citrus unshiu, Citrus depressa	Nobiletin extracted from *C. depressa* using chromatography and recrystallized in actone; dried peels of *C. reticulata* Blanco and *C. unshiu* Markovich employed as ANTII NOBILS PERICAPRIUM	Nobiletin; ANTII NOBILS PERICAPRIUM	Enhances learning and memory	*In vivo* (Mice)	(43)

Citrus derived phytochemicals, notably citric acid helps in converting the oxalates into citrates which are relatively more soluble in water and can be passed through urine. Furthermore, phytotherapy including naringenine, hesperidin and rutin have started gaining interest in recent years. Some of the study reports can be found in the references.(44-46) Table 1 lists and elaborates some of the recent scientific studies on the effects of citrus derived phytochemicals and various diseases, illness and health profiles.

The concept of consuming citrus regularly is a part of the everyday life in oriental countries. It is preserved along with peels and seeds. Cleaned citrus fruits are cut in small pieces, added with sugar, boiled for 4-7 minutes, further boiled with honey for 4-7 minutes and stored for months. It is consumed as herbal tea with hot water. Preserved honey citron tea is shown in Figure 4. Citrus is also preserved with ginger, rosemary, ginseng and other herbs for enhancing flavour and aroma as well as nutritional benefits.

Lemon Ginger Grapefruit Lemon Cherry Lemon

Figure 4. Honey citron tea. Oriental concept of preserving citrus fruits along with peels and seeds with honey and consumed as herbal tea. It is also preserved with ginger, cherry, raspberry, fig, plum, resins and other herbs for additional benefits, flavour and aroma. Furthermore, it is also freeze dried and jellied with agar agar and consumed as snacks.

CONCLUSION:

Increasing health awareness and quality of healthy life has incorporated citrus as an essential part of diet and cuisine. Citrus not only provides nutritional supplements but also helps reducing risks of several illnesses. Edible as well as non-edible parts of citrus both are rich in various phytochemical and value added compounds. Non-edible parts or citrus wastes are reused to obtain more than 400 commercial products which are either utilized in nutritional supplements, curative medicines, food processing, preservatives, or cosmetics-making, home utilities and toiletries. The ongoing research on citrus waste reuse is dedicated to minimise the hazards from direct disposal and maximise the recovery of value added products.

REFERENCES:

1. Sood S, Bansal S, Muthuraman A, Gill NS, Bali M. Therapeutic potential of Citrus medica L. peel extract in carrageenan induced inflammatory pain in rats. Research Journal of Medicinal Plants. 2009;(3);123-33.

2. Kirtikar KR, Basu BD. Indian Medicinal Plants. Dehradun; 1983;(44);115-59.

3. Peter EE, Peter JE, Nes BI, Asukwo GE. Physiochemical properties and fungi toxicity of the essential oil of Citrus medica L. against groundnut storage fungi. Turkish Journal of Botany. 2008;(32);161-4.

4. Nagaraju B, Anand SC, Ahmed N, Chandra JNNS, Ahmed F, Padmavathi GV. Antiulcer activity of aqueous extract of Citrus medica Linn. fruit against ethanol-induced ulcer in rats. Advances in Biological Research. 2012;6(1);24-9.

5. Sharma K, Mahato N, Cho MH, Lee YR.

Converting citrus wastes into value added products: Economical and environment-friendly approaches. Nutrition. 2017;(34);29-46.

6. Kaur C, Kapoor HC. Antioxidants in fruits and vegetables-the millennium's health.International Journal of Food Science & Technology. 2001;(36);703-25.

7. Vinson JA, Su X, Xubik L, Bose P. Phenol antioxidant quantity and quality in foods: Fruits. Journal of Agricultural and Food Chemistry. 2001;(49);5315-21.

8. Park J-H, Lee M, Park E. Antioxidant activity of orange flesh and peel extracted with various solvents. Preventive Nutrition and Food Science. 2014; 19(4); 291-8.

9. Billington CJ, Epstein LH, Goodwin NJ, Hill JO, Pi-Sunyer FX, Rolls BJ, Stern J, Wadden TA, Weinsier Rl, Wilson GT, Wing RR, Yanovski SZ, Hubbard VS, Hoofnagle JH, Everhart J, Harrison B. Overweight, obesity and health risks. Archives of Internal Medicine. 2000;160(7);898-904.

10. Kopelman PG. Obesity as a medical problem. Nature. 2000;404(6778);635-43.

11. http://www.who.int/mediacentre/factsheets/fs311/en/.

12. Wei K, Wang GQ, Bai X, Niu YF, Chen HP, Wen CN, Li ZH, Dong ZJ, Zuo ZL, Xiong WY, Liu JK.Structure-based optimization and biological evaluation of pancreatic lipase inhibitors as novel potential antiobesity agents. Natural Products and Bioprospecting. 2015;5(3);129-57.

13. Seyedan A, Alshawsh MA, Alshagga MA, Koosha S, Mohamed Z. Medicinal plants and their inhibitory activities against pancreatic lipase: A review. Evidence-Based Complementary and Alternative Medicine. 2015;(97); 31-43.

14. Patricia CEF, Aldo FCS, Mayela YRC, Elvira GG, Laura A, and María del RCC. Constituents identifed in hexane extract of Citrus sinensis peel and anti-Mycobacterium tuberculosis activity of some of its constituents. Journal of the Mexican Chemical Society. 2004;58(4);431-4.

15. Johnston K, Sharp P, Clifford M, Morgan L. Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. FEBS Letters. 2005;(579);1653-7.

16. C JV. Selective estrogen receptor modulation: Concept and consequences in cancer. Cancer Cell. 2004;(15);207-13.

17. Tokunaga H, Seiwa C, Yoshioka N, Mizoguchi K, Yamamoto M, Asou H, Aiso S. An extract of Chinpi, the dried peel of the citrus fruit unshiu, enhances axonal remyelination via promoting the proliferation of oligodendrocyte progenitor cells. Evidence-Based Complementary and Alternative Medicine 2016; (86);92-698 .

18. Pantsulaia I, MananaIobadze, Pantsulaia N, Chikovani T. The effect of citrus peel extracts on cytokines levels and T- regulatory cells in acute liver injury. BioMed Research International 2014;(12);78-79.

19. Shetty SB, Mahin-Syed-Ismail P, Varghese S, Thomas-George B, KandathilThajuraj P, Baby D, Haleem S, Sreedhar S, Devang DD. Antimicrobial effects of Citrus sinensis peel extracts against dental caries bacteria: An in vitro study. Journal of Clinical and Experimental Dentistry. 2016;8(1);e70-7.

20. Miyake Y, Hiramitsu M. Isolation and extraction of antimicrobial substances against oral bacteria from lemon peel. Journal of Food Science and Technology. 2011;48(5);635–9 .

21. Joma S, Rahmo A, Alnori AS, Chatty ME. The cytotoxic effect of essential oil of Syrian Citrus limon peel on human colorectal carcinoma cell line (Lim1863). Middle East Journal of Cancer. 2012;3(1);15-21.

22. Baniya S, D.R. D, Acharya A, Dangi B, Sapkota A. Cardioprotective activity of ethanolic extract of Citrus grandis (L.) Osbeck peel on

Doxorubicin and Cyclophosphamide induced cardiotoxicity in Albino rats. International Journal of Pharmaceutical Sciences and Drug Research. 2015;7(4);354-60.

23. Saalu LC, Ajayi GO, Adeneye AA, Imosemi IO, Osinubi AA. Ethanolic seed extract of grapefruit (Citrus paradisi Macfad) as an effective attenuator of Doxorubicin-induced oxidative stress in the rat heart. International Journal of Cancer Research. 2009;5(2);44.

24. Park JY, Shin MS, Kim SN, Kim HY, Kim KH, Shin KS. Polysaccharides from Korean Citrus hallabong peels inhibit angiogenesis and breast cancer cell migration. International Journal of Biological Macromolecules. 2016;(85);522–9.

25. Lim DW, Lee Y, Kim YT. Preventive effects of Citrus unshiu peel extracts on bone and lipid metabolism in OVX rats molecules. 2014;(19);783-94.

26. Adelina R, Supriati MD, Nawangsari DA, Jenie RI, Meiyanto E. Citrus reticulata's peels modulate blood cholesterol profile and increase bone density of ovariectomized rats. Indonesian Journal of Biotechnology. 2008;13(2);1092-7.

27. Sood S, Muthuraman A, Gill NS, Bali M, Sharma PD. Effect of Citrus karna peel extract on stress induced peptic ulcer in rat. Journal of Biological Sciences. 2010;10(3);19-53.

28. EduardoPadilla-Camberos, Estefania Lazcano-Díaz, JoséMiguelFlores-Fernandez, MosesS.Owolabi, KirkAllen, SocorroVillanueva-Rodríguez. Evaluation of the inhibition of carbohydrate hydrolyzing enzymes, the antioxidant activity, and the polyphenolic content of Citrus limetta peel extract. The Scientific World Journal. 2014;(12);17-60.

29. Kim G-N, Shin M-R, Shin SH, Lee AR, LeeJY, Seo BI, Kim MY, KimTH ,NohJS ,Rhee MH, Roh SS. Study of antiobesity effect through inhibition of pancreatic lipase activity of Diospyros kaki Fruit and Citrus unshiu peel. BioMed Research International 2016;(98);67-7.

30. Kumar KA, Narayani M, Subanthini, Jayakumar M. Antimicrobial activity and phytochemical analysis of citrus fruit peels - Utilization of Fruit Waste International Journal of Engineering Science and Technology 2011;3(6);5414-21.

31. Enejoh OS, Suleiman MM, Ajanusi JO, Ambali SF. Antihelminthic activity of extracts of Citrus aurantifolia (christm) fruit peels against experimental heligmosomoides bakeri in mice. Journal of Advanced Scientific Research. 2015;6(2);29-32.

32. Abdelqader A, Qauallah B, Al-Ramamneh D, Das G.Anthelmintic effects of citrus peels ethanolic extracts against Ascaridia galli. Veterinary Parasitology. 2012;188(1-2);78-84.

33. Hernawan I, Radithia D, Hadi P, Ernawati DS. Fungal inhibitory effect of Citrus Limon peel essential oil on Candida albicans. Dental Journal (Majalah Kedokteran Gigi). 2015; 48(2);84-8.

34. Suzawa M, Guo L, Pan M-H, Ho C-T, Li S. In vivo anti-carcinogenic property of a formulated citrus peel extract. Functional Foods in Health and Disease. 2014;4(3);120-9.

35. Lee J, Yang D-S, Han S-I, Yun JH, Kim I-w, Kim SJ, Kim JH. Aqueous extraction of Citrus unshiu peel induced proangiogenic effects through the FAK and ERK1/2 signaling pathway in human umbilical vein endothelial cells. Journal of Medicinal Food. 2016;19(6);569–77.

36. Chang Y-H, Seo J, Song E, Choi H-J, Shim E, Lee O, Hwang J. Bioconverted Jeju Hallabong tangor (Citrus kiyomi×ponkan) peel extracts by cytolase enhance antioxidant and anti-inflammatory capacity in RAW 264.7 cells. Nutrition Research and Practice. 2016;10(2);131-8.

37. Shin YW, Bok H-H, Jeong T-S, Bae K-H, Jeoung NH, Choi M-S, Lee SH, Park YB. Hypocholesterolemic effect of naringin associated with hepatic cholesterol regulating enzyme changes irats. International Journal for Vitamin and Nutrition Research 1999;69 (5);341-7.

38. Kim S-Y, Kim H-J, Lee M-K, Jeon S-M, Do G-M, Kwon E-Y, Cho Y-Y, Kim D-J, Jeong K-S, Park Y-B, Ha T-Y, Choi M-S . Naringin time-dependently lowers hepatic cholesterol biosynthesis and plasma cholesterol in rats fed high-fat and high-cholesterol diet. Journal of Medicinal Food. 2006;9(4);582-6.

39. Callaway TR, Carroll JA, Arthington JD, Pratt C, Edrington TS, Anderson RC, Galyean ML, Ricke SC, Crandall P, Nisbet DJ. Citrus products decrease growth of E. coli 0157:1-17 and Salmonella Typhimurium in pure culture and in fermentation with mixed ruminal microorganisms in vitro. Foodborne pathogens and disease. 2008;5(5);621-7.

40. Vinita D Apraj, Nancy S Pandita. Evaluation of skin antiaging potential of Citrus reticulata blanco peel Pharmacognosy Research. 2016;8(3);160168.

41. Sridharan B, Mehra Y, Ganesh RN, Pragasam V. Regulation of urinary crystal inhibiting proteins and inflammatory genes by lemon peel extract and formulated citrus bioflavonoids on ethylene glycol induced urolithic rats. Food and Chemical Toxicology. 2016;(94);75-84.

42. Okuyama S, Yamamoto K, Mori H, Toyoda N, Yoshimura M, Amakura Y, Yoshida T, Sugawara K, Sudo M, Nakajima M, Furukawa Y. Auraptene in the peels of Citrus kawachiensis (Kawachi Bankan) ameliorates lipopolysaccharide-induced inflammation in the mouse brain. Evidence-Based Complementary and Alternative Medicine. 2014;(40);85-03.

43. Kawahata I, Yoshida M, Sun W, Nakajima A, Lai Y, Osaka N, et al. Potent activity of nobiletin- rich Citrus reticulata peel extract to facilitate cAMP/PKA/ERK/CREB signaling associated with learning and memory in cultured hippocampal neurons: Identification of the substances responsible for the pharmacological action. Journal of Neural Transmission. 2013;120(10);1397–409.

44. Touhami M, Laroubi A, Elhabazi K, Loubna F, Zrara I, Iljahiri Y, OussamaA, Grases F, ChaitA. Lemon juice has protective activity in a rat urolithiasis model. BMC Urology. 2007;(7);18.

45. Sridharan B, Thomas SM, Ramacharya A, Nachiappa RG, Pragasam V. Citrus bioflavonods ameliorate hyperoxaluria induced renal injury and calcium oxalate crystal deposition in Winstar rats. Advanced Pharmaceutical Bulletin. 2015;(5);419-27.

46. Sridharan B, Michael ST, Arya R, Mohana RS, Ganesh RN, Vishwanathan P. Beneficial effect of Citrus limon peel aqueous methanol extract on experimentally induced urolithic rats. Pharmaceutical Biology. 2015;54(5);759-69.

■■■