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Anti-Carcinogenic Effect of Lemon & Lemon Products in Cancer Therapy: A Summary of the Evidence

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ABSTRACT

Lemon is a popular fruit that includes many helpful nutrients for humans. Accumulated proof from research shows that nutritional intake of lemon and lemon products (e.g. lemon peel, lemon grass oil, lemon extract) appears to be inversely linked to the reduced danger of numerous infectious illnesses and cancers. These helpful impacts of the lemon will be attributed to their chemical constituents in particular. Lemon contains a range of important nutrients such as vitamin C, vitamin A, carotenes of different kinds, as well as several non-nutrient phytochemicals as well as categories of flavonoid, coumarin, glucarate, monoterpenes, triterpenes and phenolic acids. There are many compounds distinctive to lemon that are comparatively uncommon in other plants, their components such as sesqui-terpene isointermedeol, geraniol, terpene, quercetin and eriocitrin have also shown anticancer activity against various cell lines. This review regularly summarized lemon's anticarcinogenic effect in cancer therapy along with the fundamental molecular mechanisms needed to further explore the more efficient use of lemon peel, lemon grass oil, lemon extract.

KEYWORDS: *lemon; anti-cancer; vitamin C; flavonoids; limonoids*

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INTRODUCTION

Cancer is one of the world's major causes of death. It is assessed that by 2025, there will be an expanded rate of 19.3 million new cases every year [1]. Diet is believed to play a vital role in four major diseases of advanced and transitional economies: cardiovascular disease, cancer, high blood pressure, and obesity. The degree to that diet is very important in the interference of these diseases is not known. However, a commonly accepted estimate among specialists is that at least one-third of cancer cases are attributed to diet and perhaps one-half of the cases of heart and artery diseases and high blood pressure are associated with diet [2] [3].

Food plays a vital role in cancer development and progression and recent studies showed a clear correlation between reduced cancer risk and the consumption of high fiber, low-fat diets [4] [5]. Additionally, several natural dietary products exhibit anticancer activity by completely different mechanisms, as well as metastasis inhibition, immune system activation, apoptosis induction, and augmenting therapeutic effects of anticancer agents [6] [7] [8]. Citrus fruits are rich in biologically active compounds that may inhibit cancer. Recent studies established the anticancer activity of citrus peels with superior activity reported for lemon peels [9]. Additionally, daily consumption of citrus fruits is related to reduce risk for gastric cancer [10].

Citrus (such as lemon) is one of the necessary fruits of high medicinal value and has long been the basis of commonly used traditional medicines in many Asian countries [11]. Along with these, citrus fruits are widely used in cuisine materials as salad dressing, sauces, jams, and vinegar as well as whole fresh fruits. The meditative and industrial importance of those merchandise ends up in intensive scientific study leading to broad base data of their chemical composition and bioactivities. These beneficial impacts of citrus fruits can be attributed in particular to their chemical components, including vitamins, dietary fiber, carotenoids, flavonoids, lipids and essential oils [12] [13].

MAJOR CHEMICAL CONSTITUENTS OF LEMON WITH ANTICANCER PROPERTIES

A. Limonoids

Citrus limonoids are accountable for the bitter taste in citrus fruits. The most prevalent limonoids are limonin and nomilin (Figure 1). They are available in the rutaceous plants that include lemon, orange, lime, and grapefruits. A vital

characteristic of this class of compound is a substituted furan moiety. It has been determined by animal studies that citrus limonoids and derivatives have certain biological activities that may be used as chemo preventive agents for cancer. [14] [15].

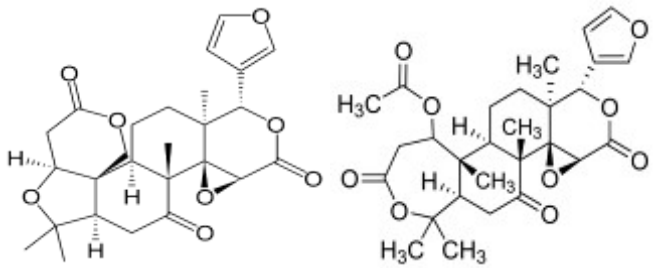

Figure 1: Chemical structure of (a) limonin and (b) nomilin, the major bioactive limonoids.

Glutathione S-transferase (GST) is a major detoxifying enzyme system that catalyzes the conjugation of glutathione with electrophiles that induce activated carcinogens. The glutathione conjugates are usually less reactive and more water-soluble, and hence, facilitate excretion. A rise in GST activity caused by a substance is, therefore, an elevation in the mechanism that protects against the noxious effects of xenobiotics, including carcinogens. It has been discovered that many chemicals that are GST enhancers inhibit chemically induced carcinogenesis [15] [16].

B. Flavonoids

Flavonoid structure is based on a 2-phenyl-benzo[a]pyrane or flavane nucleus. This nucleus is defined by having a system of two benzene rings (A and B), which are connected by an oxygen-containing pyrane ring (C). The flavonoids (including compounds such as flavones, isoflavones, flavonols and flavanes) are a group of low molecular weight polyphenolic compounds that are widely distributed in plants oxidative processes contributing to immediate tissue damage that occurs during heart attack or stroke (Figure 2) [17] [18] [19].

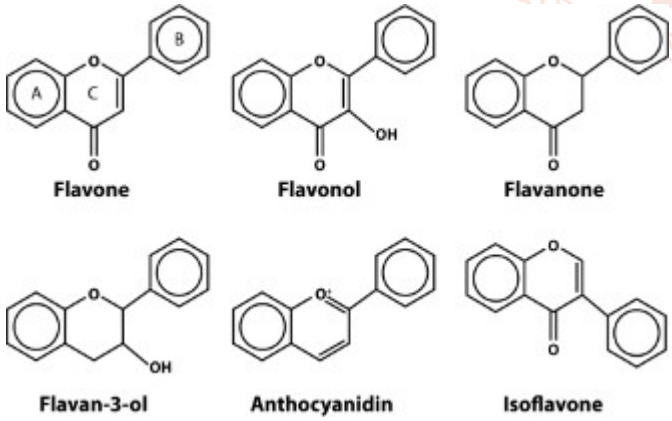

Figure 2: Chemical structures of sub-classes of flavonoids.

C. Vitamin C (ascorbic acid)

Vitamin C is an important water-soluble antioxidant (Figure-3) in biological fluids. It promptly scavenges reactive nitrogen and oxygen species, for example, hydroperoxyl radicals, superoxide, singlet oxygen, aqueous peroxyl radicals, peroxynitrite, ozone, nitrogen dioxide, nitroxide radicals, and hydrochlorous acid, thereby essentially protecting other biomolecules from oxidative damage. Vitamin C can also behave as a coantioxidant by regenerating α-tocopherol (vitamin E) from the α-tocopheroxyl radical generated via scavenging of lipid-soluble radicals. This is a potentially important significant because in vitro experiments have shown that α-tocopherol can behave as a pro-oxidant in the absence of co-antioxidants such as vitamin C [20] [21] [22] [14] [15] [16].

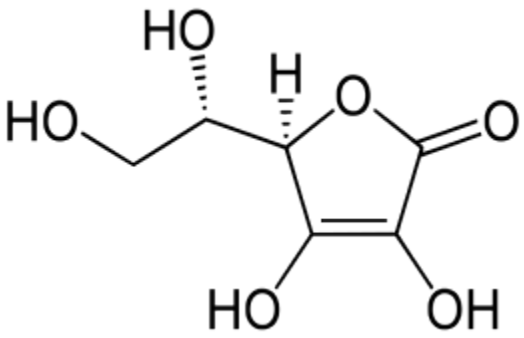

Figure 3: Chemical structure of ascorbic acid (antioxidant).

Vitamin C may protect against cancer through several mechanisms, in addition to inhibiting DNA oxidation. One potential mechanism is chemoprotection against mutagenic compounds such as nitrosamines, which can be formed by the reaction of nitrite or nitrate (common in food and cigarette smoke) with amines and amides.26,27 Vitamin C prevents the reaction of nitrites with amines and amides that form potent carcinogenic nitrosamines within the digestive tract and prevents oxidation of specific chemicals to their active carcinogenic forms [18] [19] [23].

D. Essential oils

Citrus (lemon) essential oil comes from the fruits and leaves of various citrus species. It may be either steam processed or cold-pressed to produce the essential oil. Fruits and vegetables contain an abundance of terpenoids, phenolic substances and different natural anti-oxidants that are associated with protection from and treatment of chronic diseases like cancer and disorder. It has been shown that terpenoids in the category of citrus compounds are useful in maintaining and improving health, including several subclasses such as monoterpenes terpene, carvone, myrcene, and carveol), sesquiterpenes β-cubebene, β-elemene, β-caryophyllene, π-cadinene, diterpenes retinoids, oleanic acid, and ursolic acid). These subclasses have a range of action mechanisms that influence oxidative stress, carcinogenesis, and cardiovascular diseases, among others [24].

E. Coumarins

Coumarins possess anti-carcinogenic activities partially by inducing carcinogen detoxifying enzymes. By causing carcinogenic detoxifying enzymes, naturally occurring coumarins have anti-carcinogenic operations in part. Citrus peels comprise a range of coumarins that possess mevalonate derived side chains with numerous oxidation levels. Citrus peels contain a variety of coumarins that possess mevalonate derived side chains with numerous oxidation levels. Researchers have demonstrated that orally administered citrus coumarin, limettin, imperatorin and isopimpinellin blocked 7, 12-dimethylbenz anthracene DMBA) DNA adduct formation in mouse mammary glands (Prince, et al., 2006). Interestingly, citrus oils, specifically, contain extensive amounts of both simple as well as

furanocoumarins. three known citrus coumarins particularly bergamottin, oxypeucedanin and 5-[6, 7-dihydroxy-3, 7-dimethyl-2-octenyl) oxy] psoralen, have been isolated from Citrus hystrix DC as inhibitors of both lipopolysaccharide LPS) and interferon- IFN-γ)-induced nitric oxide NO) generation in RAW 264.7 cells. Consequently, suppression of the iNOS-induced NO generation in excess amounts is currently accepted wide as a new paradigm for the chemoprevention of cancer [25].

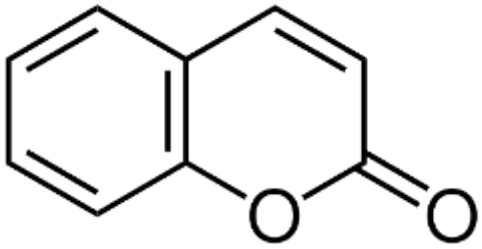

Figure 4: Chemical structure of coumarins

F. Citrus fatty acids

Citrus fruits (lemon) are well-known to be an abundant resource of compounds that might help prevent lifestyle-related diseases like diabetes, high pressure, and cancer. Many fatty acids were reported from the seed and peel of citrus species [26]. Antioxidant activity of the citrus extract is additionally assessed by measuring free fatty acid content since unsaturated fatty acids play a very important role to regulate the various sorts of cancers. The constituents of total lipids and neutral lipid categories, i.e., hydrocarbons, wax esters, sterol esters, triacylglycerols, free fatty acids, 1,3-diacylglycerols, 1,2-diacylglycerols, free sterols, alcohols, and monoacylglycerols of 3 species of Citrus particularly *C. sinensis, C. paradisi, C. aurantium* were investigated by thin layer and gas natural process. Palmitic, oleic and linoleic acids were the main elements in all the lipids and lipid categories studied [27].

ANTICANCER ROLE OF LEMON & LEMON PRODUCTS

A. Lemon

Numerous epidemiological findings and investigations have demonstrated that consumption of vegetables and fruits decreased the incidence of carcinogenesis [28] [29]. Therefore, it is feasible to find novel drugs in dietary phytochemicals to interfere with the development of cancer [30]. Lemon (*Citrus Limon*) belongs to citrus fruits. It contains various polyphenols (mainly flavonoids) which possess positive health effects, for instance, the amelioration of behavioral impairment, anti-oxidation, and cancer prevention [31] [32] [33] [34] [35]. Eriocitrin (eriodictyol 7-rutinoside) is such a flavonoid extracted from lemon. Minato et al. reported that eriocitrin could protect diabetic rats from oxidative stress, suggesting that it may serve as an antioxidative agent in vivo [36]. Hiramitsu et al. found that eriocitrin suppressed exercise-induced oxidative damage in rat liver as well [37]. In addition, Wang et al. showed that eriocitrin could ameliorate diet-induced hepatic steatosis [38]. Interestingly, the structure of eriocitrin is very similar to hesperidin, which was reported to exhibit antitumor effects on various cancers such as liver cancer and ovary cancer [34]

[38]. Thus, we speculated that eriocitrin may also have anticancer activity and examined whether eriocitrin could inhibit the proliferation of hepatocellular carcinoma cells.

B. Lemon (Citrus lemon L.) peel extract

Lemon is a vital healthful plant of the family Rutaceae. It is harvested primarily for its alkaloids, which are having anticancer activities and the antibacterial potential in crude extracts of various components (leaves, stem, viz., root and flower) of lemon against clinically significant microorganism strains has been reported [39]. The depart Citrus fruits (*Citrus lemon* L.) could be a wealthy supply of flavonoid glycosides, coumarins, β and γ- sitosterol, glycosides and volatile oils [40]. Several polymethoxylated flavones have many necessary bioactivities that are very rare in other plants [41]. Citrus flavonoids have a wide range of biological activity including antibacterial, antidiabetic, antifungal, anticancer and antiviral activities [42] [43]. Flavonoids can perform as direct antioxidants and radical scavengers, and have the capability to modulate protein activities and inhibit cell proliferation [44]. In plants, they seem to play a defensive role against invasive pathogens, including bacterium, fungi, and viruses [45].

C. Lemon grass oil

Several natural products are nowadays used as effective anticancer agents. Within the last 20 years, the search for novel anticancer agents from natural sources has witnessed an impressive increase of interest. The genus *Cymbopogon* (family *Gramineae)* has several species of grasses that grow in tropical and semitropical regions around the world from mountains to grasslands to arid zones [46]. These plants produce essential oils with pleasant aromas in their leaves. Five species yield the three oils of main commercial importance: lemongrass from *Cymbopogon citratus* of Malaysian origin (West Indian lemongrass) and *Cymbopogon flexuosus* (East Indian lemongrass) from India, Sri Lanka, Burma, and Thailand; palmarosa oil from *Cymbopogon martinii*; citronella oil from *Cymbopogon nardus* (Sri Lanka), and *Cymbopogon winterianus* (Java). *Cymbopogon flexuosus* (also referred to as East India or Cochin lemongrass) is a perennial, multicut aromatic grass that yields a necessary oil used in perfumery and pharmaceutical industries and vitamin A [47]. *Cymbopogon flexuosus* oil helps with stress-related disorders, and has shown to own antifungal and antimicrobial properties [48]. The chemical composition of the oil has additionally been reported [49]. The various constituents (%) present in the oil from lemongrass variety of *C. flexuosus* like geraniol (20.08), geranyl acetate (12.20), α-bisabolol (8.42) and isointermedeol (24.97) are one by one reported for his or her neoplastic cell toxicity [49] [50].The volatile oil from a lemongrass kind of *Cymbopogon flexuosus* (CFO) and its major chemical constituent sesqui-terpene isointermedeol (ISO) were investigated for their ability to induce apoptosis in human leukemia HL-60 cells because deregulation of apoptosis is the hallmark of cancer cells. CFO and ISO suppressed cell proliferation with IC50 of ~30 and 20 μg/ml, respectively [49].

D. Lemon extract

Lemon extract contains many biologically active phytochemicals including D-limonene. This compound is a monocyclic monoterpene and represents a major component of citrus oils [51]. Inductions of apoptosis and angiogenesis inhibition are the main mechanisms of action of limonene against cancer [52]. In the present study, high concentrations of limonene were recognized in the combination as well as lemon extract. The observed anticancer effect of the lemon extract could be explained by the presence of high

concentrations of limonene in lemon extract. Phytochemical analysis revealed the presence of phenolic compounds, flavonoids, and alkaloids in lemon aqueous extract [53]. These results are consistent with the previous study that showed the presence of phenols, alkaloids, flavonoids, and terpenoids in lemon juice. A dose-dependent inhibition of cell growth and proliferation was observed after treatment of EMT6/P cells with serial dilutions of lemon aqueous extract (30–100 mg/mL) with IC50 value of 89.32 mg/mL [54].

CONCLUSION

Taken all together, a considerable number of well-established lines of evidence have confirmed that citrus fruits (e.g. lemon, lemon peel, lemon grass oil, lemon extract) exhibit a remarkable spectrum of efficacious biological activities, particularly in antitumori genesis. As mentioned earlier, the d-limonene found in citrus fruits has multiple health advantages and one of them includes cancer prevention. Lemons also contain a flavonoid, which, according to a recent study, has strong cancer-preventing properties. Lemon peel, lemon extract and lemon grass oil also contain high amounts of flavonoid, monoterpenes, triterpenes, sesquiterpene isointermedeol, which are plant compounds found to prevent tumors cell. Lemons, lemon peel, lemon grass oil, the lemon extract have to possess great bioavailability which consequently attracts researchers to perform scientific studies for effective disease prevention and treatment.

AUTHOR'S CONTRIBUTION

Mohammad Asadul Habib carried out the studies, participated in the sequence alignment, performed in the analysis of the findings and drafted the manuscript. Md. Al Amin in the design of the study, sequence alignment & drafted the manuscript. Kawsar Hossen; Assistant Professor, Noakhali Science & Technology University conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

REFERENCES

[1] Block KI, Gyllenhaal C, Lowe L, Amedei A, Amin AR, Amin A, Aquilano K, Arbiser J, Arreola A, Arzumanyan A, Ashraf SS. Designing a broad-spectrum integrative approach for cancer prevention and treatment. InSeminars in cancer biology 2015 Dec 1 (Vol. 35, pp. S276-S304). Academic Press

[2] Goldberg I. Functional foods: designer foods, pharmafoods, nutraceuticals. Springer Science & Business Media; 2012 Dec 6.

[3] Milner JA. Reducing the Risk of Cancer [w:] Functional Food, pod red. I. Goldberg.

[4] Zhou Y, Li Y, Zhou T, Zheng J, Li S, Li HB. Dietary natural products for prevention and treatment of liver cancer. Nutrients. 2016 Mar;8(3):156.

[5] Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C. Fruit and vegetables and cancer risk: a review of southern European studies. British Journal of Nutrition. 2015 Apr;113(S2):S102-10.

[6] J Thoppil R, Bhatia D, F Barnes K, Haznagy-Radnai E, Hohmann J, S Darvesh A, Bishayee A. Black currant anthocyanins abrogate oxidative stress through Nrf2-mediated antioxidant mechanisms in a rat model of hepatocellular carcinoma. Current cancer drug targets. 2012 Nov 1; 12(9):1244-57.

[7] Yu MH, Gwon Im H, Gyu Lee S, Kim DI, Jeong Seo H, Lee IS. Inhibitory effect of immature plum on PMA-induced MMP-9 expression in human hepatocellular carcinoma. Natural product research. 2009 May 20; 23(8):704-18.

[8] Ren M, Ye L, Hao X, Ren Z, Ren S, Xu K, Li J. Polysaccharides from Tricholoma matsutake and Lentinus edodes enhance 5-fluorouracil-mediated H22 cell growth inhibition. Journal of Traditional Chinese Medicine. 2014 Jun 1;34(3):309-16.

[9] Alshatwi AA, Shafi G, Hasan TN, Al-Hazzani AA, Alsaif MA, Alfawaz MA, Lei KY, Munshi A. Apoptosis-mediated inhibition of human breast cancer cell proliferation by lemon citrus extract. Asian Pac J Cancer Prev. 2011 Jan 1;12(6):1-555.

[10] Bae JM, Kim EH. Dietary intakes of citrus fruit and risk of gastric cancer incidence: an adaptive metaanalysis of cohort studies. Epidemiology and health. 2016;38.

[11] Kubo M, Matsuda H, Tomohiro N, Harima S. Historical and pharmalogical study of Citrus hassaku. Yakushigaku zasshi. 2005;40(1):47-51.

[12] Patil JR, Jayaprakasha GK, Murthy KC, Tichy SE, Chetti MB, Patil BS. Apoptosis-mediated proliferation inhibition of human colon cancer cells by volatile principles of Citrus aurantifolia. Food Chemistry. 2009 Jun 15;114(4):1351-8.

[13] Hardin A, Crandall PG, Stankus T. Essential oils and antioxidants derived from citrus by-products in food protection and medicine: an introduction and review of recent literature. Journal of Agricultural & Food Information. 2010 Apr 14;11(2):99-122.

[14] Miller EG, Gonzales-Sanders AP, Couvillon AM, Binnie WH, Hasegawa S, Lam LK. Citrus limonoids as inhibitors of oral carcinogenesis. Food technology (USA). 1994.

[15] Lam LK. Citrus limonoid reduction of chemically-induced tumorigenesis. Food. Technol.. 1994;48:104-8

[16] Brody T. Digestion and absorption of carbohydrates, u Nutritional Biochemistry (T. Brody, urednik).

[17] Aruoma OI. Free radicals, oxidative stress, and antioxidants in human health and disease. Journal of the American oil chemists' society. 1998 Feb;75(2):199-212.

[18] Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. The American journal of clinical nutrition. 1999 Jun 1;69(6):1086-107.

[19] Silalahi J. Free radicals and antioxidant vitamins in degenerative diseases. J Indon Med Assoc. 2001;51:16-21.

[20] Gillman MW. Enjoy your fruits and vegetables

[21] Zino S, Skeaff M, Williams S, Mann J. Randomised controlled trial of effect of fruit and vegetable consumption on plasma concentrations of lipids and antioxidants. Bmj. 1997 Jun 21;314(7097):1787.

[22] Burri BJ. Beta-carotene and human health: a review of current research. Nutrition Research. 1997 Mar 1;17(3):547-80.

[23] Rouseff RL, Nagy S. Health and nutritional benefits of citrus fruit components. Food technology (USA). 1994.

[24] Wagner KH, Elmadfa I. Biological relevance of terpenoids. Annals of Nutrition and metabolism. 2003;47(3-4):95-106.

[25] Murakami A, Gao G, Kim OK, Omura M, Yano M, Ito C, Furukawa H, Jiwajinda S, Koshimizu K, Ohigashi H. Identification of coumarins from the fruit of Citrus hystrix DC as inhibitors of nitric oxide generation in mouse macrophage RAW 264.7 cells. Journal of agricultural and food chemistry. 1999 Jan 18;47(1):333-9.

[26] Saidani M, Dhifi W, Marzouk B. Lipid evaluation of some Tunisian Citrus seeds. Journal of Food Lipids. 2004 Sep;11(3):242-50.

[27] Waheed A, Mahmud S, Saleem M, Ahmad T. Fatty acid composition of neutral lipid: Classes of Citrus seed oil. Journal of Saudi Chemical Society. 2009 Oct 1;13(3):269-72.

[28] Key TJ. Fruit and vegetables and cancer risk. British journal of cancer. 2011 Jan;104(1):6-11.

[29] Reddy LA, Odhav B, Bhoola KD. Natural products for cancer prevention: a global perspective. Pharmacology & therapeutics. 2003 Jul 1;99(1):1-3.

[30] Lee KW, Bode AM, Dong Z. Molecular targets of phytochemicals for cancer prevention. Nature Reviews Cancer. 2011 Mar;11(3):211.

[31] González-Molina E, Domínguez-Perles R, Moreno DA, García-Viguera C. Natural bioactive compounds of Citrus limon for food and health. Journal of pharmaceutical and biomedical analysis. 2010 Jan 20;51(2):327-45.

[32] Li C, Zug C, Qu H, Schluesener H, Zhang Z. Hesperidin ameliorates behavioral impairments and neuropathology of transgenic APP/PS1 mice. Behavioural brain research. 2015 Mar 15;281:32-42.

[33] Bacanlı M, Başaran AA, Başaran N. The antioxidant and antigenotoxic properties of citrus phenolics limonene and naringin. Food and chemical Toxicology. 2015 Jul 1;81:160-70.

[34] Banjerdpongchai R, Wudtiwai B, Khaw-on P, Rachakhom W, Duangnil N, Kongtawelert P. Hesperidin from Citrus seed induces human hepatocellular carcinoma HepG2 cell apoptosis via both mitochondrial and death receptor pathways. Tumor Biology. 2016 Jan 1;37(1):227-37.

[35] Miyake Y, Yamamoto K, Tsujihara N, Osawa T. Protective effects of lemon flavonoids on oxidative stress in diabetic rats. Lipids. 1998 Jul 1;33(7):689.

[36] Minato KI, Miyake Y, Fukumoto S, Yamamoto K, Kato Y, Shimomura Y, Osawa T. Lemon flavonoid, eriocitrin, suppresses exercise-induced oxidative damage in rat liver. Life sciences. 2003 Feb 21;72(14):1609-16.

[37] Hiramitsu M, Shimada Y, Kuroyanagi J, Inoue T, Katagiri T, Zang L, Nishimura Y, Nishimura N, Tanaka T. Eriocitrin ameliorates diet-induced hepatic steatosis with activation of mitochondrial biogenesis. Scientific reports. 2014 Jan 15;4:3708.

[38] Wang Y, Yu H, Zhang J, Gao J, Ge X, Lou G. Hesperidin inhibits HeLa cell proliferation through apoptosis mediated by endoplasmic reticulum stress pathways and cell cycle arrest. BMC cancer. 2015 Dec;15(1):682.

[39] Kawaii S, Tomono Y, Katase E, Ogawa K, Yano M, Koizumi M, Ito C, Furukawa H. Quantitative study of flavonoids in leaves of Citrus plants. Journal of agricultural and food chemistry. 2000 Sep 18;48(9):3865-71.

[40] Shahnah SM, Ali S, Ansari H, Bagri P. New sequiterpene derivative from fruit peel of citrus limon (Linn) Burn. F. Sci. Pharm. 2007;75:165-70.

[41] Ahmad MM, Iqbal Z, Anjum FM, Sultan JI. Genetic variability to essential oil composition in four citrus fruit species. Pakistan Journal of Botany. 2006 Feb;38(2):319.

[42] Burt S. Essential oils: their antibacterial properties and potential applications in foods—a review. International journal of food microbiology. 2004 Aug 1;94(3):223-53.

[43] Ortuño A, Báidez A, Gómez P, Arcas MC, Porras I, García-Lidón A, Del Río JA. Citrus paradisi and Citrus sinensis flavonoids: Their influence in the defence mechanism against Penicillium digitatum. Food Chemistry. 2006 Jan 1;98(2):351-8.

[44] Duthie G, Crozier A. Plant-derived phenolic antioxidants. Current opinion in lipidology. 2000 Feb 1;11(1):43-7.

[45] Sohn HY, Son KH, Kwon CS, Kwon GS, Kang SS. Antimicrobial and cytotoxic activity of 18 prenylated flavonoids isolated from medicinal plants: Morus alba L., Morus mongolica Schneider, Broussnetia papyrifera (L.) Vent, Sophora flavescens Ait and Echinosophora koreensis Nakai. Phytomedicine. 2004 Nov 25;11(7-8):666-72.

[46] Kumar S, Dwivedi S, Kukreja AK, Sharma JR, Bagchi GD. Cymbopogon: The aromatic grass monograph. Lucknow, India: Central Institute of Medicinal and Aromatic Plants; 2000.

[47] LEWINSOHN E, DUDAI N, TADMOR Y, KATZIR I, Ravid UZ, Putievsky EL, JOEL DM. Histochemical localization of citral accumulation in lemongrass leaves (Cymbopogon citratus (DC.) Stapf., Poaceae). Annals of Botany. 1998 Jan 1;81(1):35-9.

[48] Chao SC, Young DG, Oberg CJ. Screening for inhibitory activity of essential oils on selected bacteria, fungi and viruses. Journal of essential oil research. 2000 Sep 1;12(5):639-49.

[49] Kumar A, Malik F, Bhushan S, Sethi VK, Shahi AK, Taneja SC, Qazi GN, Singh J. An essential oil and its major constituent isointermedeol induce apoptosis by increased expression of mitochondrial cytochrome c and apical death receptors in human leukaemia HL-60 cells. Chemico-biological interactions. 2008 Feb 15; 171(3):332-47.

[50] Cavalieri E, Mariotto S, Fabrizi C, de Prati AC, Gottardo R, Leone S, Berra LV, Lauro GM, Ciampa AR, Suzuki H.

α-Bisabolol, a nontoxic natural compound, strongly induces apoptosis in glioma cells. Biochemical and biophysical research communications. 2004 Mar 12; 315(3):589-94.

[51] Lu XG, Zhan LB, Feng BA, Qu MY, Yu LH, Xie JH. Inhibition of growth and metastasis of human gastric cancer implanted in nude mice by d-limonene. World Journal of Gastroenterology: WJG. 2004 Jul 15; 10(14):2140.

[52] Njoku VI, Evbuomwan BO. Analysis and comparative study of essential oil extracted from Nigerian orange, lemon and lime peels. Greener Journal of Chemical Science and Technology. 2014;1(1):6- 14.

[53] Oikeh EI, Omoregie ES, Oviasogie FE, Oriakhi K. Phytochemical, antimicrobial, and antioxidant activities of different citrus juice concentrates. Food science & nutrition. 2016 Jan;4(1):103-9.

[54] Talib WH. Consumption of garlic and lemon aqueous extracts combination reduces tumor burden by angiogenesis inhibition, apoptosis induction, and immune system modulation. Nutrition. 2017 Nov 1; 43:89-97.